

TITLE PAGE

Title:	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
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Investigational New Drug (IND) Number:	142031
Development Phase:	Phase II

This study will be conducted in compliance with ICH Good Clinical Practice and Standard Operating Procedures of Laekna Limited or its designee for all processes involved, including the archiving of essential documents.

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SPONSOR SIGNATORY

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

I, the undersigned, have reviewed and approved version 6.0 of the clinical study protocol with the date of 23 January 2023.



Yong Yue, MD, PhD
Chief Medical Officer
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23 January, 2023

Date

INVESTIGATOR PROTOCOL AGREEMENT

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

I confirm agreement to conduct the study in compliance with the protocol.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALL	Acute lymphocytic leukemia
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
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
β-HCG	Beta-human chorionic gonadotropin
BICR	Blinded Independent Central Review
BOR	Best overall response
BP	Blood pressure
BUN	Blood urea nitrogen
CA-125	Cancer antigen-125
CBC	Complete blood count
CCOC	Clear cell ovarian cancer
CI	Confidence interval
CL/F	Apparent clearance
CLL	Chronic lymphocytic leukemia
C _{max}	Maximum concentration (after first dose)
C _{max_SS}	Maximum concentration at steady state
CPK	Creatine phosphokinase
CR	Complete response
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
C _t	Plasma drug concentration at a specified time t after the administration of a given dose
CT	Computed tomography
C _{trough_SS}	Trough concentration at steady state
CYP	Cytochrome P450
D	Day
DCR	Disease control rate

DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ENOC	Endometrioid ovarian cancer
EOT	End of treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FSH	Follicle-stimulating hormone
FTIH	First-time-in-human
f/u	Follow-up
GCIG	Gynecological Cancer Intergroup
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HGSOC	High-grade serous ovarian cancer
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IC ₅₀	Half maximal inhibitory concentration
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product

IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive web response system
Ki	Inhibitory constant
LDH	Lactate dehydrogenase
LGSOC	Low-grade serous ovarian cancer
LPLV	Last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MOC	Mucinous ovarian cancer
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mechanistic target of rapamycin
NA	Not applicable
NAE	Not all evaluated
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not evaluable
NGS	Next generation sequencing
N _{max}	Maximum number of patients per treatment arm
OC	Ovarian cancer
ORR	Overall response rate
OS	Overall survival
PARP	Poly ADP ribose polymerase
PARPi	Poly ADP ribose polymerase inhibitor
PAS	Pharmacokinetics Analysis Set
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3 kinase
PK	Pharmacokinetic(s)
PO	Per os (oral)
PopPK	Population PK
PP	Predictive probability

PPoS	Predicted Probability of Success
PR	Partial response
PROC	Platinum-resistant ovarian cancer
PT	Prothrombin time
PTEN	Phosphatase and tensin analog protein
PTT	Partial thromboplastin time
Q3W	Every 3 weeks / three-weekly
QD	Once daily
QTcF	QT interval by the Fridericia's correction formula
QW	Once weekly
R	Randomization
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase II dose
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvate transaminase
SRC	Safety Review Committee
T _{1/2}	Apparent terminal half-life
TEAE	Treatment-emergent adverse event
θ_L	Threshold probability to stop for futility
θ_T	Threshold probability to declare efficacy
T _{max}	Time to maximum concentration (after first dose)
T _{max_SS}	Time to maximum concentration at steady state
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
ULRR	Upper limit of reference range
US	United States
VGPR	Very good partial response
WBC	White blood cell(s)
WHO	World Health Organization

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Short Title:

Afuresertib Plus Paclitaxel Versus Paclitaxel in Platinum-Resistant Ovarian Cancer

Rationale:

Ovarian cancer (OC; including fallopian tube and primary peritoneal cancers because of their common Müllerian epithelium derivation and similar management) is the seventh most commonly diagnosed cancer among women in the world. OCs account for an estimated 239,000 new cases and 152,000 deaths worldwide annually. Unfortunately, despite frequent initial response to chemotherapy, these tumors almost invariably relapse.

The first-line standard of care adjuvant therapy for patients with newly diagnosed OC is platinum and taxane therapy (category 1 recommendation) either with or without bevacizumab (category 2B recommendation).¹ If used in combination with carboplatin and paclitaxel following initial surgical resection, bevacizumab monotherapy is typically continued as maintenance therapy. Poly ADP ribose polymerase (PARP) inhibitors are also prescribed as maintenance therapy for OC patients who respond to platinum-based therapy.

The initial treatment for platinum-resistant OC (PROC) is typically a chemotherapy regimen consisting of either weekly paclitaxel with an overall response rate (ORR) ranging from 20.9% to 28.8%^{2,3,4} and a median progression-free survival (PFS) from 3.5 to 3.9 months in PROC patients who had received only one prior platinum-based therapy^{2,3,4}, or topotecan with a median PFS of 5.0 months in PROC patients who had received one prior platinum-based therapy^{2,5}, or gemcitabine with an ORR of 15% to 20% and a PFS of 4.0 months in Phase II studies in PROC patients with one or two prior platinum-based therapies, or pegylated liposomal doxorubicin.^{6,7} A clinical study reported that the weekly paclitaxel regimen, at the dose of 80 mg/m²/week, had a better efficacy (ORR 27%, PFS 7.0 months, overall survival [OS] 15.5 months) and tolerability/safety in PROC as compared to the traditional paclitaxel every three weeks (ORR 16%, PFS 4.5 months, OS 12.5 months).⁸

The third- or later-line treatments for PROC have a PFS of 3 to 4 months and a limited ORR of between 10% and 15%.^{9,10,11} Rucaparib was approved by the Food and Drug Administration (FDA) as a third- or fourth-line therapy with a PFS of 7.3 months and an ORR of 25% in PROC patients with germline or somatic BRCA mutations. The PFS of the control arms (treated with

paclitaxel alone, without bevacizumab) was 3.9 months in the Phase III AURELIA trial (3.4 months for average of 3 chemotherapies)², and 3.5 months in the Lortholary et al. trial.^{3,4} Therefore, the median PFS with paclitaxel in multiple lines setting from 6 clinical trials averaged 3.5 months⁴³. These PFS results may be an appropriate benchmark for the control arm in the present Phase II study exploring the addition of afuresertib to weekly paclitaxel. However, the study population in the above studies were different from the patient population in this Phase II study because the current Phase II study targets the PROC patients who have had 1 to 5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed. In addition, patients in the current study may or may not have been treated with bevacizumab previously. The PROC patients treated with weekly paclitaxel alone in the above historical controls had either at least 1 prior platinum-based therapy or 1 to 4 prior non-platinum-based treatments. Therefore, the real historically comparable control PFS for the current Phase II study is unknown, but would logically be closer to the lower end of the PFS range (3.5 months) based on the above 3 studies.^{2,3,4} A randomized, open-label, parallel, two-arm design is the best way to assess the efficacy and safety of the combination therapy of afuresertib plus weekly paclitaxel versus weekly paclitaxel in this study. Currently, there are limited treatment options in clinical management for PROC patients who have had 1 to 5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed and who may or may not have been treated with bevacizumab previously. This indication is a major unmet medical need and highlights the urgent need to develop new combination therapy.

AKT inhibitors are a new class of agents under development that may provide physicians with a new clinical option to control PROC progression. Preclinical studies suggest that increased AKT activity could be a primary mechanism of resistance to platinum and taxane therapy, and that resistance can be reversed by AKT inhibitors.^{12,13,14} Afuresertib (LAE002, GSK2110183), a new oral, small-molecule pan-AKT kinase inhibitor, can reduce AKT activity in cancer cells and re-sensitize tumor cells to platinum or taxane when used as a combination therapy.¹⁵ In addition, afuresertib plus chemotherapy has demonstrated anti-tumor efficacy and an acceptable safety profile in patients with PROC in a published Phase I/II study.¹⁶ Therefore, the combination of afuresertib plus weekly paclitaxel could represent a clinically meaningful step forward in the clinical management of these difficult-to-treat patients with PROC.

Objectives and Endpoints:

Evaluation of the different combination therapies for PROC:

Objectives	Endpoints
Primary	
To evaluate the clinical efficacy of afuresertib plus weekly paclitaxel versus weekly paclitaxel in patients with PROC	PFS based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
Secondary	
To further evaluate the clinical efficacy of afuresertib plus weekly paclitaxel versus weekly paclitaxel in patients with PROC	- 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])
- 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	- 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 ($C_{trough_{ss}}$)
To evaluate the safety and tolerability of afuresertib plus weekly paclitaxel or weekly paclitaxel in patients with PROC	- The evaluation of safety and tolerability will be based on, but not limited to, the following parameters: - Rate and severity of treatment-emergent adverse events (TEAEs) based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 - Vital signs - Electrocardiogram (ECG) - Physical examinations - Laboratory tests

Objectives	Endpoints
Exploratory	
- To explore the efficacy of the combination treatment arm 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)	- Efficacy of the combination treatment arm versus paclitaxel arm in the biomarker-defined subpopulations by the following endpoints: - 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)
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	PopPK analysis will be described in a separate analysis plan and reported separately from the Clinical Study Report (CSR)
To conduct exploratory metabolite analysis of afuresertib in PK samples remaining after quantification of afuresertib / paclitaxel	Metabolite analysis and / or quantification will be described in a report separately from the CSR.

Study Hypothesis:

In the Phase III AURELIA trial, PROC patients who had previously received first-line platinum-based therapy had ORRs of 27.3% versus 11.8% (average of the 3 chemotherapies based on RECIST v1.1) when treated with bevacizumab + chemotherapy versus chemotherapy alone, respectively. However, the study population in the above study was different from the patient population in this Phase II study because the current Phase II study targets the PROC patients who have had 1 to 5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed. In addition, patients may or may not have been treated with bevacizumab previously. The PROC patients treated with weekly paclitaxel alone in the above historical control had either at least 1 prior platinum-based therapy or 1 to 4 prior non-platinum-based treatments. Therefore, the real historically comparable control PFS for the current Phase II study is unknown, but would logically be closer to the lower end of the PFS range (3.5 months) based on the above 3 studies.^{2,3,4} A randomized, open-label, parallel two-arm design is the best way to assess the efficacy and safety of the combination therapy with afuresertib plus weekly paclitaxel versus weekly paclitaxel in this study. Therefore, with the reasonable justification, the estimated historical PFS is about 3.5 months in PROC patients treated with weekly paclitaxel alone from 3 clinical studies as mentioned above.^{2,3,4}

The study combination therapy of afuresertib plus weekly paclitaxel lacks historical reference since there is no clinical study of this combination therapy conducted in PROC patients. However, the Novartis Phase I/II study can be used as the reference study for the current Phase II study, although the combination treatment in the Novartis Phase I/II study was a triple

combination therapy of afuresertib plus paclitaxel (Q3W) plus carboplatin (Q3W), whereas the combination therapy in the current Phase II study is afuresertib plus weekly paclitaxel. In addition, the study populations in both studies are similar, in that the Phase I/II study enrolled patients with 1-7 prior lines of treatments, and the current Phase II study will enroll PROC patients who have had 1-5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed. Therefore, it is expected that the planned Phase II Study LAE002INT2001 will have a PFS of approximately 6.5 months in the PROC population which is shorter than that from the Novartis Phase I/II Study PKB116611 because treatment with afuresertib plus weekly paclitaxel may have a slightly lower efficacy as compared to the PFS of 7.1 months in the Novartis Phase I/II study using triple combination therapy of afuresertib plus paclitaxel (Q3W) plus carboplatin (Q3W).¹⁶

The study will test the following hypotheses:

$$H_0: \text{PFS}_{\text{comb}} = \text{PFS}_{\text{ctrl}} \text{ versus } H_a: \text{PFS}_{\text{comb}} \neq \text{PFS}_{\text{ctrl}} .$$

Study Design:

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 vs. 3-5 prior platinum regimens). The study will consist of 3 periods. The first period is the Screening Period (Day -24 to -1) during which patients are screened for eligibility according to the inclusion and exclusion criteria. The second period is a Treatment Evaluation Period with a randomized, open-label, two-arm parallel design (from starting study treatment until patients have progressive disease [PD], unacceptable toxicity, death, or withdrawal of consent). The PK study will be applied to both the combination treatment arm and control arm. The third period is a Follow-up Period (safety evaluation at 30 days after the last dose of study treatment and OS and/or PFS follow-up). Patients will be tested at baseline for phosphoinositide 3 kinase (PI3K)/AKT/PTEN pathway alterations and BRCA1/2 mutations by NGS, and/or level of phospho-AKT by IHC; the correlation of the efficacy endpoints and biomarker status will be analyzed retrospectively as an exploratory endpoint.

After screening, 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 over 1 hour on Days 1, 8 and 15 of a 3-week cycle.
- Arm 2 is paclitaxel 80 mg/m² IV infusion over 1 hour on Days 1, 8, and 15 of a 3-week cycle.

Patients must have had 1 to 5 prior chemotherapies 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 maintenance therapy following chemotherapy. 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.

Afuresertib monotherapy was not selected as a treatment arm because monotherapy of AKT inhibitor may not kill cancer cells due to its mechanism of action. In addition, several clinical trials of other AKT inhibitors, such as ipatasertib (Roche) and capivasertib (AstraZeneca), demonstrated that the combination therapies of AKT inhibitors with other agents, rather than being used as a monotherapy, had clinically meaningful efficacy in different cancers. Novartis reported that afuresertib monotherapy showed limited clinical benefit in patients with advanced hematological malignancies (most patients with multiple myeloma [MM]) in a Phase I study with an ORR of 8.8% (3/34 patients).^{17,18} However, the combination therapy of afuresertib with bortezomib + dexamethasone demonstrated significantly greater efficacy (ORR 53.3%, in 48/90 patients) in a Phase I/II study in patients with recurrent MM.^{17,19} Therefore, based on these clinical results, as well as preclinical results and the presumed mechanism of action, afuresertib monotherapy was not selected as one of the testing arms in this study.

Sample size estimation and statistical analysis methodology:

The primary endpoint of this study is PFS. Previous studies^{2,3,4} have shown that PROC patients have a median PFS of around 3.5 months with weekly paclitaxel after 1 to 5 prior chemotherapies including no more than one chemotherapy after 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.

Considering a censoring rate of 25%, a total number of 141 patients (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.

Study Assessments:

Safety and tolerability of the therapies in the Treatment Evaluation Period will be evaluated by TEAEs, adverse events (AEs) and serious adverse events (SAEs), dose reduction or delays, withdrawals due to toxicities and changes in laboratory values and vital signs. PFS, defined as the time from random assignment in a clinical trial to disease progression or death due to any reason, will be assessed using RECIST 1.1 as the primary endpoint. The study has a randomized open-label design and the comparison of the endpoints will be carried out between 2 arms.

1.2 Schema

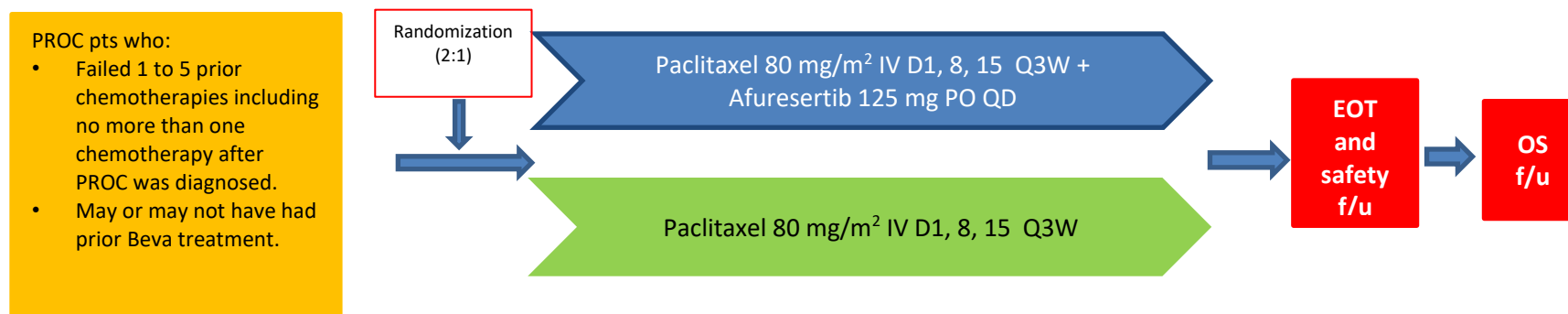


Figure 1. Study Design Schema

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.

2 INTRODUCTION

2.1 Background

Ovarian cancer (OC), including fallopian tube, or primary peritoneal cancers, is the seventh most commonly diagnosed cancer among women in the world. OCs account for an estimated 239,000 new cases and 152,000 deaths worldwide annually.²⁰ An estimated 52,100 new cases and 22,500 OC deaths in China and 22,440 new cases and 14,080 OC-related deaths in the USA were estimated in 2017.^{21,22} High-grade serous OC (HGSOC) accounting for up to 70% of all epithelial Ocs, clear cell OC (CCOC) 10%, endometrioid OC (ENOC) 10%, mucinous OC (MOC) 3%, and low-grade serous OC (LGSOC) 5%, are the major histotypes of epithelial Ocs.²³ HGSOC, CCOC, and ENOC will be the histotypes of OC in this study.

OC is the most lethal cause of gynecological cancer deaths in the developing world and typically 70% of patients with OC are diagnosed at an advanced stage due to absence of symptoms in the early stages and lack of a reliable screening test for OC.²⁴ Platinum- and taxane-based chemotherapy with or without bevacizumab is the initial standard therapy administered postoperatively.¹ The treatments for platinum-resistant ovarian cancer (PROC) are usually non-platinum-based chemotherapy in the second-line or later-line setting, such as weekly taxanes, which have demonstrated an overall response rate (ORR) of 20.9% to 28.8% and progression-free survival (PFS) from 3.5 to 3.9 months^{2,3,4} and other non-platinum regimens that have limited responses (ORR ranging from 10% to 15%) and PFS of 3.4 to 5.1 months.^{9,11,12,13,14,17} Although significant headway has been recently made in our understanding of the molecular pathogenesis of OC, these advances have not yet translated into meaningful clinical benefit for patients.²⁵ The only two approved novel targeted therapies to date in PROC are bevacizumab and rucaparib. Rucaparib is a poly ADP ribose polymerase (PARP) inhibitor approved as the third- and fourth-line therapy for PROC patients who have germline or somatic BRCA mutations. ARIEL2 was a global, multicenter, two-part, Phase II, open-label study that included patients with PROC with a ORR of 25% and PFS of 7.3 months.²⁶ In the Phase III AURELIA trial of 662 patients with PROC, bevacizumab administration provided an improvement in PFS to 6.7 months from 3.4 months (in the paclitaxel-alone subgroup: ORR = 28.8% and PFS = 3.9 months) for those assigned to chemotherapy alone.² Therefore, developing new targeted therapy is a critical unmet medical need for patients with PROC.

The phosphoinositide 3 kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) cascade is probably the most frequently altered signaling pathway in a variety of cancers, including OC. AKT is a serine/threonine kinase that regulates a large number of downstream targets^{27,28}, while the phosphatase and tensin analog protein (PTEN) acts as an endogenous pathway repressor by dephosphorylating PIP3 back to PIP2. AKT controls critical cellular survival and metabolic processes by influencing many of the cell cycle and cell growth signaling pathways. In addition to activation via upstream input, the PI3K pathway can be ‘intrinsically’ activated due to: i) gain of function mutations or amplifications in the p110 subunit of PI3K (PIK3CA), ii) alterations in one of the AKT isoforms (AKT1, AKT2, AKT3), or iii) loss of its negative regulator, PTEN via inactivating mutations, copy number loss, or homozygous deletions.²⁹

In HGSOc, oncogenic mutations are rare, but amplifications of the p110 subunit of PI3K (PIK3CA) have been described in 20% of cases, amplifications of one of the AKT isoforms (AKT1, AKT2 or AKT3) occur in 15% to 20% of cases, while PTEN deletions have been described in 7% of cases.^{30,31} PIK3CA amplification and PTEN loss is associated with platinum non-response, phospho-AKT amplification in HGSOc, ENOC, and CCOC histology of OC. These observations indicate the PI3K/AKT pathway plays a critical role in the chemoresistance of different types of OC histology.¹³ Another study reported that the treatment of OC cells with paclitaxel also induces AKT phosphorylation, which prevents taxane-induced apoptosis.¹⁴ AKT is activated with platinum treatment in PROC cells, and AKT inhibitors (but not PI3K inhibitors) restore platinum sensitivity to these cells.¹⁵

Afuresertib (LAE002, GSK2110183) is an oral, small-molecule pan-AKT kinase inhibitor that has demonstrated activity in hematologic and solid tumor cell lines. It also has the ability to delay tumor growth in a dose-dependent manner in solid tumor xenograft models. A detailed summary of in vitro and in vivo nonclinical pharmacology studies is provided in the afuresertib Investigator's Brochure (IB).¹⁷ Furthermore, afuresertib has demonstrated anti-tumor efficacy and safety in several previous studies ([Section 2.2.1](#), [Section 2.2.2](#), and [Section 2.2.3](#)).

2.2 Afuresertib Clinical Data

2.2.1 Results of First-Time-in-Human Study PKB112835 in Hematologic Malignancies

PKB112835 was a first-time-in-human (FTIH), Phase I, open-label, two-stage study to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of afuresertib in patients with hematologic malignancies. In the dose-escalation phase, afuresertib was administered once daily (QD) at doses of 25 mg, 75 mg, 100 mg, 125 mg, or 150 mg. Additional patients were enrolled in the expansion cohort at the maximum tolerated dose (MTD) (125 mg QD) to further define the safety and tolerability of the identified MTD. A total of 73 patients were enrolled in study PKB112835. Patients had the following tumor types at study entry: non-Hodgkin lymphoma (13 patients), Hodgkin's lymphoma (8 patients), Langerhans cell histiocytosis (1 patient), chronic lymphocytic leukemia (CLL) (7 patients), multiple myeloma (MM) (34 patients), acute lymphocytic leukemia (ALL) (1 patient), and acute myeloid leukemia (AML) (9 patients).

Following single doses of afuresertib in the dose-escalation phase, plasma concentrations were measured for all patients over the 72-hour sample collection period ([Table 1](#)). Mean accumulation with multiple doses was approximately 3-fold for all dose levels. Mean area under the curve from time 0 to 24 hours (AUC_{0-24}) and maximum concentration (C_{max}) values increased with increasing doses; however, given the size of the inter-patient variability, there was substantial overlap in the AUC_{0-24} and C_{max} values between successive dose groups. The 100 mg and 125 mg multiple dose exposure data were similar. Median time to maximum concentration (T_{max}) across doses were in the range of 1.5 to 2.5 hours post-dose. Based on available data from all cohorts in the dose-escalation phase of the study, the mean half-life ($T_{1/2}$) values after single doses were 33-41 hours, resulting in approximately 3-fold accumulation at steady state.

Table 1. Mean ± Standard Deviation Afuresertib Plasma PK Parameters after Multiple Ascending Doses

Dose	C _{max} ng/mL	T _{max} hr	AUC(0-τ) ng*hr/mL	Accum %	CL/F L/hr	C _t 0,8 ng/mL	C _t 24,8 ng/mL	C _t 0,15 ng/mL
25 mg (N=2)	68.6 ± 15.9	2.46 (1.92, 3.00)	1141.6 ± 354.82	320.5 ± 24.11	23.0 ± 7.15	33.6 ± 4.38	45.7 ± 8.63	45.2 ± 4.03
75 mg (N=2)	248 ± 5.66	1.50 (1.00, 2.00)	3107.5 ± 120.69	291.9 ± 37.49	24.2 ± 0.938	124 ± 43.3	132 ± 14.8	114 ± 24.1
100 mg (N=8)	554 ± 198	2.50 (1.00, 8.00)	6782.4 ± 2004.0	326.0 ± 158.0	16.5 ± 7.25	249 ± 107	248 ± 102	261 ± 162
125 mg (N=8)	531 ± 288	2.00 (1.00, 7.90)	7405.3 ± 3584.0	286.1 ± 66.90	21.7 ± 13.2	259 ± 105	236 ± 125	342 ± 172
150 mg (N=6)	949 ± 348	2.00 (1.92, 3.00)	13425 ± 3952.6	301.1 ± 131.9	12.4 ± 5.37	624 ± 345	459 ± 173	822 ± 576

Note: T_{max} is presented as median (min, max).

There were not enough data in the terminal phase or a poor regression to calculate T_{1/2} and V_{dss/F} at all mg dose levels on Day 8.

AUC = Area under the curve during a dosage interval; C_{max} = Maximum concentration; CL/F = Clearance; C_t = Plasma drug concentration at a specified time t after the administration of a given dose; PK = Pharmacokinetic; T_{max} = Time to maximum concentration; V_{dss/F} = Apparent volume of distribution at steady state.

The most common adverse events (Aes; occurring in ≥20% of patients regardless of causality) were nausea (36.6%), diarrhea (32.9%), dyspepsia (24.7%), and fatigue (20.5%).

Two dose-limiting toxicities (DLTs) of elevated liver enzymes were observed in 2 patients receiving 150 mg afuresertib. Of note, one of the patients had a diagnosis of mantle-cell lymphoma or follicular lymphoma. The MTD for QD dosing of afuresertib was identified as 125 mg.

The most common (occurring in ≥10% of patients when rounding the percentage to the nearest whole number) grade 3 or higher AEs were anemia (9.6%) and neutropenia (9.6%). Twenty patients reported serious adverse events (SAEs); the majority of SAEs were considered not related to treatment with afuresertib. Three deaths were reported, none of which were considered related to study treatment.

Afuresertib demonstrated clinical activity across a range of hematologic malignancies with the activity best characterized in patients with MM.

2.2.2 Results of Study PKB115125 (Combination of Afuresertib, Bortezomib and Dexamethasone) in Multiple Myeloma

PKB115125 was a two-part, Phase Ib study to evaluate the safety, tolerability, PK, pharmacodynamics, and clinical activity of afuresertib administered in combination with bortezomib and dexamethasone in patients with relapsed/refractory MM. Part 1 was designed to identify the MTD(s) of the combination regimen/schedule using a 3 + 3 dose escalation procedure. Part 2 was designed to further explore the safety, tolerability, PK, pharmacodynamics, and clinical activity of the MTD(s) identified in Part 1.

A total of 90 patients were enrolled and administered at least 1 dose of afuresertib. In the dose-escalation part (Part 1), 34 patients were administered doses of afuresertib ranging from 75 to 175 mg/day, in combination with bortezomib and dexamethasone.

Table 2 lists the dosing cohorts that have cleared dose escalation in Part 1 with ≤ 1 out of 6 patients per cohort experiencing a DLT.

Table 2. Dosing Cohorts that Cleared Dose Escalation in Part 1 of Study PKB115125

Afuresertib (oral daily)	Bortezomib (IV, Days 1, 4, 8 and 11 every 21 days)	Dexamethasone (oral on days of bortezomib administration)	Patients (n)	DLT
75 mg	1.0 mg/m ²	20 mg	4	None
100 mg	1.3 mg/m ²	20 mg	6	1 patient with grade 2 abdominal pain and grade 2 elevation in ALT
125 mg	1.3 mg/m ²	20 mg	6	1 patient with grade 3 erythema multiforme
150 mg	1.3 mg/m ²	20 mg	6	none
175 mg	1.3 mg/m ²	20 mg	6	2 patients (1 patient with grade 3 rash and 1 patient with grade 3 diarrhea)

ALT = Alanine aminotransferase; DLT = Dose-limiting toxicity; IV = Intravenous

Part 2 enrolled 56 patients at a dose of 150 mg of afuresertib (the MTD) QD in combination with bortezomib (1.3 mg/m² on Days 1, 4, 8 and 11 of 21-day cycles) and dexamethasone (20 mg on days of bortezomib administration).

For patients enrolled in Part 2 of the study and treated with the MTD, grade 3, 4 and 5 AEs were reported in 23 patients (50%), 12 patients (26%), and 2 patients (4%), respectively. The most frequently reported grade 3 event ($\geq 20\%$ incidence) was diarrhea (10 patients).

Thrombocytopenia was the most frequent grade 4 AE reported in 7 patients (15%). Two patients had grade 5 AEs of pneumonia and respiratory failure reported in 1 patient each. See the afuresertib IB for additional details.¹⁷

In part 2, one patient (2%) achieved stringent complete response (CR), 5 patients (11%) had CR, 9 patients (20%) had very good partial response (VGPR), and 15 patients (33%) had partial response (PR). The ORR (95% confidence interval [CI]) was 65% (49.8%, 78.6%).

In the PKB115125 study, sparse samples for PK were obtained starting with Cycle 2 Day 1 and continued on Day 1 for an additional 4 cycles. Co-administration with bortezomib and dexamethasone in PKB115125 resulted in a decrease in area under the curve in the inter-dose interval period after first dose (AUC_{τ}) of afuresertib most likely due to the induction of CYP3A4 by dexamethasone. The AUC_{τ} of afuresertib alone was 23% higher than that of afuresertib

combined with bortezomib and dexamethasone. Considering the variability in the PK parameters of afuresertib this change was not considered clinically meaningful.

2.2.3 Results of Study PKB116611 (Combination of Afuresertib, Paclitaxel, and Carboplatin) in PROC

The Phase I/II study PKB116611 evaluated afuresertib in patients with PROC in combination with paclitaxel and carboplatin. The recommended dose for co-administration of afuresertib was 125 mg QD with paclitaxel and carboplatin for 6 cycles, which was continued beyond completion of the 6 cycles of the combination therapy as maintenance monotherapy at the dose of 150 mg QD.

At least one grade 3 or higher AE was reported for 76.3% of patients. The blood and lymphatic (37.3%), gastrointestinal (GI; 22.0%), and skin (23.7%) system organ classes accounted for most of these higher-grade treatment-emergent AEs. SAEs were reported in 52.5% of patients, the majority of which were either GI or infectious in nature.

Of the 28 recurrent patients with PROC in the Phase II part of the study, the ORR with confirmation defined by Response Evaluation Criteria in Solid Tumors (RECIST) was 32.1% (95% confidence interval [CI]: 15.9, 52.4). Median PFS was 7.1 months (95% CI: 6.3, 9.0). The results suggested that the addition of afuresertib may re-engage platinum sensitivity in patients with recurrent PROC who have previously acquired resistance to platinum and/or taxane therapies and therefore represents a potentially valuable treatment option for those patients.

2.3 Study Rationale

Preclinical studies suggest that increased AKT activity could be a primary mechanism of resistance to platinum and taxane therapy, and that resistance can be reversed by AKT inhibitors.^{12,13,14} Given the poor prognosis of patients with PROC and the potential role of AKT activation after platinum-based therapy, and the preliminary efficacy of paclitaxel, carboplatin and afuresertib combination observed in clinical studies conducted in patients with PROC (Novartis Phase I/II Study PKB116611), as well as the treatment effect of paclitaxel and afuresertib combination in a previously conducted gastric cancer study¹⁷, the combination of an AKT inhibitor plus paclitaxel in PROC patients who failed the prior platinum-based therapy warrants further testing. The therapeutic roles of AKT inhibitor plus paclitaxel in those PROC patients with either alterations in the PI3K/AKT/PTEN pathway and/or median/high levels of phospho-AKT will also be explored in this study. 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 chemotherapies (no more than one chemotherapy after PROC was diagnosed) with or without prior bevacizumab treatment. It is critical to understand the safety and anticancer efficacy of the afuresertib plus weekly paclitaxel combination. The main purpose of Study LAE002INT2001 is to evaluate the safety and efficacy of the 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.

2.4 Dose Rationale

2.4.1 Afuresertib

The dose of afuresertib to be given as combination therapy in this study will be 125 mg daily per os (PO) (Section 6.1.1). In the Phase II extension part of Study PKB116611, afuresertib was safely administered to 30 patients with PROC at dose level of 125 mg daily alongside clinically standard doses of carboplatin and paclitaxel chemotherapy.

2.4.2 Weekly Paclitaxel

The dose of paclitaxel to be given as combination therapy in this study will be 80 mg/m² weekly as an infusion over 1 hour (Section 6.2.1). A clinical study reported that the weekly paclitaxel regimen, at the dose of 80 mg/m²/week, had a better efficacy (ORR 27%, PFS 7.0 months, overall survival [OS] 15.5 months) and tolerability/safety in PROC as compared to the traditional paclitaxel every three weeks (ORR 16%, PFS 4.5 months, OS 12.5 months).⁸ In addition, Novartis conducted a Phase Ib clinical study to assess the efficacy and safety of the recommended Phase II dose (RP2D) of afuresertib 200 mg QD plus paclitaxel (80 mg/m²/week for 3 weeks every 4 weeks) in 21 patients with paclitaxel-resistant, Her2 (-) advanced gastric cancer. The ORR was 33.3% in these advanced gastric cancer patients at the RP2D with acceptable tolerability and safety profiles.¹⁷ The dose of afuresertib in this current Phase II study with PROC patients is 125 mg QD, which is much lower than the 200 mg QD dose in the gastric cancer study mentioned above. The lower dose of afuresertib may have a better tolerability and safety profile in PROC patients as compared to those in the gastric cancer study. Therefore, weekly paclitaxel plus afuresertib may have a better safety and similar efficacy profile compared to the three drug combination in the previous Phase I/II Study PKB116611 in PROC patients.

2.5 Summary of Risk Management

Risk has been assessed based on (1) nonclinical studies and the clinical experience from the completed single-agent afuresertib PKB115125 trial and combination PKB116611 trial of afuresertib + paclitaxel and carboplatin, (2) the AE profile documented in the product information for paclitaxel, and (3) the AE profile observed with Q3W carboplatin and paclitaxel in a Phase III trial and a Novartis/GSK Phase I study in patients with OC.^{16,32}

2.5.1 Predicted Overlapping Toxicities

Hematologic Toxicity:

Bone marrow suppression, including grade 3/4 toxicities, has been observed with single-agent paclitaxel and afuresertib. In Study PKB116611, blood and lymphatic system AEs occurred in 37 of 59 patients (62.7%), including 20 (33.9%) with neutropenia, 16 (27.1%) with anemia, and 14 (23.7%) with thrombocytopenia. Neutropenia was the most frequent grade 4 treatment-emergent adverse event (TEAE) and was reported in 10 (16.9%) patients. In addition, the most common TEAEs leading to discontinuation of study treatment that occurred in ≥ 5% of patients included neutropenia (13 patients, 22.0%), thrombocytopenia (7 patients, 11.9%).

Complete blood counts (CBC) will be measured frequently during therapy to monitor

hematologic toxicity. Supportive therapy will be provided according to standard medical practice. Cases of grade 3 or 4 neutropenia and/or grade 3 thrombocytopenia plus bleeding during the study should be reported to the Medical Monitor for his/her review to decide whether these patients could remain in the study. Treatment continuation will be based on the investigator's clinical judgment of the symptoms, physical examination, laboratory tests, or other necessary clinical examinations. Dose adjustment/stopping criteria related to hematologic toxicity are provided in [Section 6.8](#).

Gastrointestinal (GI) Toxicity:

Diarrhea, nausea and vomiting have been observed in patients taking single-agent paclitaxel and single-agent afuresertib. Diarrhea is one of the major AEs observed in previous studies. Medical history, continuous assessment of AEs, physical examination, and clinical laboratory assessments will be used to identify and assess toxicity in the GI tract. Supportive therapy will be provided according to standard medical practice. Guidelines and recommendations for GI toxicity management are provided in [Section 6.9](#). Treatment will be discontinued for clinically significant toxicity. The investigator, based on his/her clinical judgement, may consider giving the preventive treatments to patients with potential high risk of diarrhea.

2.5.2 Other Toxicities Based on Clinical Experience**Metabolic Toxicity:**

Both hypoglycemia and hyperglycemia have been observed in patients taking afuresertib. While paclitaxel is not expected to cause glucose abnormalities, steroids given in combination with paclitaxel to decrease the frequency of hypersensitivity reactions and chemotherapy-induced emesis can cause steroid-induced diabetes. Glucose monitoring will be implemented through the whole therapy process, according to the clinical judgement by the investigator. If hyperglycemia is observed, supportive therapy will be provided according to standard medical practice, and dose reduction or treatment discontinuation will follow recommendations provided in [Section 6.8.4](#).

Hypersensitivity Reactions:

Hypersensitivity reactions have been observed with paclitaxel and increase in frequency with repeated exposure, particularly with platinum. Supportive care regimens involving steroids, antihistamines, H₂ receptor antagonists, and changes in infusion rates will be implemented per standard medical practice. If necessary, desensitization protocols may be considered. Patients with severe reactions including hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria will not be rechallenged. Dose modification guidelines are provided in [Section 6.8](#) and drug will be discontinued for clinically significant toxicity.

Nervous System:

Grade 3/4 peripheral neuropathy has been observed in patients treated with paclitaxel. Afuresertib is not expected to exacerbate this toxicity. Patients with pre-existing neuropathy

greater than grade 2 at screening will not be allowed to participate. Dose modification guidelines are provided in [Section 6.8](#) and drug will be discontinued for clinically significant toxicity.

2.5.3 Potential Clinically Significant Drug-Drug Interactions

Afuresertib:

In vitro data indicate that afuresertib has the potential of being a perpetrator in drug-drug interactions through enzyme inhibition (with substrates of cytochrome P450 [CYP] 3A4 and 2C8, half maximal inhibitory concentration [IC₅₀] estimates of 3.7 to 6.0 μ M [1.6 to 2.6 μ g/mL] and 6.3 μ M [2.7 μ g/mL], respectively) and transporter inhibition (with substrates of OATP1B1 and BCRP [ABCG2], IC₅₀ estimates of 1.7 μ M [0.7 μ g/mL] and 2.9 μ M [1.2 μ g/mL]). Co-administration of afuresertib and medications that are a sensitive substrate of CYP3A4, OATP1B1, and BCRP with low therapeutic index will be prohibited. Co-administration of afuresertib and medications that are a sensitive substrate of CYP2C8, such as repaglinide, with low therapeutic index will be used with caution.³³

In vitro data indicate that afuresertib has the potential of being a victim in drug-drug interactions through CYP3A4 and to a lesser extent CYP2D6 and CYP1A2. It is also a substrate for both P-glycoprotein (P-gp) and BCRP. Substances that potently inhibit or induce these enzymes/transporters could lead to alterations in the pharmacologic effects of afuresertib and potentially much higher/lower exposure in patients.

Preliminary clinical data suggest that C_{max} plasma concentrations following repeat-dose afuresertib at 125 mg and 150 mg ranged from 228 to 874 ng/mL and from 485 to 1280 ng/mL, respectively. The maximum 125 mg values range from 1.9- to 3.1-fold lower than the CYP IC₅₀ values and ranged from 0.8- to 1.4-fold lower than the transporter IC₅₀ values.

Paclitaxel:

In vitro data indicate that paclitaxel has the potential of being a perpetrator in drug-drug interaction through enzyme inhibition with CYP3A4 at inhibitory constant (K_i) values of 5 to 10 μ M or 4.3 to 8.5 μ g/mL³⁴, which are within the possible range of plasma concentrations that could be observed in this study.

Paclitaxel is a substrate for metabolism by CYP2C8 and CYP3A4 and transport by P-gp. The median afuresertib C_{max} value in the FTIH study at 125 mg, the highest proposed dose in the present study, was 531 ng/mL and this value is 3- to 5-fold lower than the in vitro IC₅₀ values predicted for CYP3A4 and CYP2C8 inhibition by afuresertib. While this analysis suggests there is a safety margin between the exposures of afuresertib predicted to occur at 125 mg and those that would be predicted to influence paclitaxel exposures, there is a possibility of a drug-drug interaction between the two drugs.

3 OBJECTIVES AND ENDPOINTS

Evaluation of the different combination therapies for PROC:

Objectives	Endpoints
Primary	
To evaluate the clinical efficacy of afuresertib plus weekly paclitaxel versus weekly paclitaxel in patients with PROC	PFS based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
Secondary	
To further evaluate the clinical efficacy of afuresertib plus weekly paclitaxel versus weekly paclitaxel in patients with PROC	- 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])
- 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	- 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 ($C_{trough_{ss}}$)
To evaluate the safety and tolerability of afuresertib plus weekly paclitaxel or weekly paclitaxel in patients with PROC	- The evaluation of safety and tolerability will be based on, but not limited to, the following parameters: - Rate and severity of treatment-emergent adverse events (TEAEs) based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 - Vital signs - Electrocardiogram (ECG) - Physical examinations - Laboratory tests

Objectives	Endpoints
Exploratory	
• To explore the efficacy of the combination treatment arm 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)	• Efficacy of the combination treatment arm versus paclitaxel arm in the biomarker-defined subpopulations by the following endpoints: ○ 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)
• 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	• PopPK analysis will be described in a separate analysis plan and reported separately from the Clinical Study Report (CSR)
• To conduct exploratory metabolite(s) analysis of afuresertib in PK samples remaining after quantification of afuresertib / paclitaxel	• Metabolite analysis and / or quantification will be described in a report separately from the CSR.

4 STUDY DESIGN

4.1 Overall Design

The study design is graphically presented in [Section 1.2](#).

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 vs. 3-5 prior platinum regimens). The study will consist of 3 periods. The first period is the Screening Period (Day -24 to -1) during which patients are screened for eligibility according to the inclusion and exclusion criteria. The second period is a Treatment Evaluation Period with a randomized, open-label, two-arm parallel design (from starting study treatment until patients have progressive disease [PD], unacceptable toxicity, death, or withdrawal of consent). PK samples will be collected following either a sparse or serial sampling scheme ([Section 4.1.1](#)). The PK study will be applied to both the combination treatment arm and the control arm. The third period is a Follow-up Period (safety evaluation at 30 days after the last dose of study treatment and OS and/or PFS follow-up). Patients will be tested at baseline for PI3K/AKT/PTEN pathway alterations and BRCA1/2 mutations by NGS, and/or level of phospho-AKT by IHC; the correlation of the efficacy endpoints and biomarker status will be analyzed retrospectively as an exploratory endpoint.

After screening, 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 Days 1, 8, and 15 of a 3-week cycle.
- Arm 2 is paclitaxel 80 mg/m² IV infusion in 1 hour on Days 1, 8, and 15 of a 3-week cycle.

Patients must have had 1 to 5 prior 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. No more than one chemotherapy is allowed after the PROC was diagnosed. 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.

Afuresertib monotherapy is not selected as a treatment arm because monotherapy of AKT inhibitor may not kill cancer cells due to its mechanism of action. In addition, several clinical trials of other AKT inhibitors, such as ipatasertib (Roche) and capivasertib (AstraZeneca), demonstrated that the combination therapies of AKT inhibitors with other agents, rather than being used as a monotherapy, had clinically meaningful efficacy in different cancers. Novartis

reported that afuresertib monotherapy showed limited clinical benefit in patients with advanced hematological malignancies (most patients with MM) in a Phase I study with an ORR of 8.8% (3/34 patients).^{17,18} However, the combination therapy of afuresertib with bortezomib + dexamethasone demonstrated a significantly greater efficacy (ORR 53.3%, in 48/90 patients) in a Phase I/II study in patients with recurrent MM.^{17,19} Therefore, based on these clinical results, as well as preclinical results and the presumed mechanism of action, afuresertib monotherapy was not selected as one of the testing arms in this study.

Details of sample size estimation and statistical analysis methodology are provided in [Section 10](#).

4.1.1 Pharmacokinetic Sampling

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:

In Arm 1, at the first combination therapy day (Cycle 1 Day 1), blood samples for PK analysis of afuresertib and paclitaxel will be obtained at pre-dose and at 1 (at the end of paclitaxel infusion), 2, 3, 4, 8 and 24 hours post-dose. At repeat dosing (Cycle 2 Day 1), blood samples for PK analysis of afuresertib and paclitaxel will be obtained pre-dose and at 0.5, 1 (at the end of paclitaxel infusion), 2, 3, 4, 8 and 24 hours post-dose.

In Arm 2, at repeat dosing (Cycle 2 Day 1), blood samples for PK analysis of paclitaxel will be obtained predose and at 0.5, 1 (at the end of paclitaxel infusion), 2, 3, 4, 8 and 24 hours postdose.

For all patients in Arm 1, $C_{\text{trough,SS}}$ PK samples for afuresertib will be obtained pre-dose on Cycle 3 Day 1 and Cycle 4 Day 1.

5 PATIENT SELECTION AND DISCONTINUATION/COMPLETION CRITERIA

5.1 Patient Selection Criteria

5.1.1 Number of Patients

The study plans to randomize around 141 patients diagnosed with PROC.

5.1.2 Inclusion Criteria

Waivers for inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the eligibility criteria as specified in the protocol is essential.

Patients eligible for enrollment in the study must meet all the following criteria:

1. Female patients at least 18 years of age at the time of signing the informed consent form and capable of giving written informed consent, which includes willingness to comply with the requirements and restrictions listed in the consent form.
2. Must provide informed consent for the procedures and the tests for PI3K/AKT/PTEN pathway alterations, BRCA1/2 mutations, and/or level of phospho-AKT. The archival tumor biopsy sample collected less than 1 year is preferred. If no archival tumor sample is available, fresh biopsy will be recommended. (Note: Core biopsy should not be performed within 7 days prior to Study Day 1.) For patients who cannot provide a tumor sample or cannot accept fresh tumor biopsy, the Sponsor should be consulted about their qualification to enter this study.
3. Patients must have histologically or cytologically confirmed high-grade serous OC, endometrioid OC, or ovarian clear cell carcinoma (including fallopian tube and primary peritoneal cancers). Carcinosarcoma, sarcoma, mucinous OC, or low-grade serous OC or the other histologies must be excluded.
4. Must not have previously received prior AKT or PI3K pathway or mTOR inhibitors.
5. Must have PROC (including fallopian tube and primary peritoneal carcinoma), defined as disease relapsed between 1 to 6 months after the last dose of the first-line platinum-based therapy (at least 3 cycles), or progressed during or relapsed within 6 months of the last dose of platinum-based 2nd-5th line therapies.
6. The OC patients must have received 1 to 5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed. Combination therapy with two or more drugs will be considered as one therapy, whereas maintenance therapy will be considered as continuation of the previous systemic treatment.
7. Patients should be appropriate candidates for treatment with single agent weekly paclitaxel based on investigator's clinical assessment.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
9. Must meet the following criteria for hematology parameters:
 - Absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$
 - Platelets $\geq 100,000/\mu\text{L}$

- Hemoglobin ≥ 9.0 g/dL
10. Total serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) (in patients with known Gilbert's syndrome, total bilirubin $\leq 3 \times$ ULN with direct bilirubin $\leq 1.5 \times$ ULN).
 11. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT])/alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase [SGPT]) must be $< 2.5 \times$ institutional ULN. For patients with liver metastasis, AST/ALT must be $< 5.0 \times$ institutional ULN.
 12. Creatinine within $1.5 \times$ ULN or creatinine clearance > 30 mL/min by Cockcroft-Gault formula (Appendix 1).
 13. Toxicities of prior therapy (except alopecia) should have been resolved to less than or equal to grade 1 as per NCI-CTCAE v5.0.
 14. Patients must have GI functions that would allow absorption of afuresertib.
 15. Patient must have a life expectancy of greater than 6 months.
 16. Must have at least one lesion that meets the definition of measurable disease by RECIST 1.1 criteria (Appendix 3).
 17. Patients of childbearing potential must agree to use adequate contraception (barrier method of birth control or abstinence) prior to study entry and for the duration of study participation. If a woman becomes pregnant or suspects she is pregnant while participating in this study, she should inform her treating physician immediately.
 18. Must be off strong inhibitors or inducers of CYP3A4/5 treatment, as showed in Appendix 2, for at least 2 weeks from Study Day 1.

5.1.3 Exclusion Criteria

Waivers for the exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Patients meeting any of the following criteria must not be enrolled in the study:

1. Primary platinum-refractory disease, defined as “disease progression during or relapsed within 1 month after the last dose of the first-line platinum-based therapy”.
2. Known or suspected brain metastases.
3. Receiving any other anticancer therapeutic agents other than study medicines.
4. Uncontrolled ascites, defined as “patients who presented with > 500 ml of ascites at screening; or has required paracentesis in the 3 months prior to screening, and/or is anticipated to require paracentesis during the study, to remove > 500 mL of ascites on a regular basis”.
5. Known symptomatic or impending cord compression, except if the patient has received definitive treatment for this and demonstrates evidence of clinically stable disease.
6. Presence of other active cancer within 3 years prior to enrollment (other than basal cell or squamous cell skin cancer, or any other cancer in situ currently in complete remission).
7. History of seizure or condition that may predispose to seizure that needs anti-epileptic medications; brain arteriovenous malformation; or intracranial masses, such as schwannomas and meningiomas that are causing edema or mass effect.

8. Known allergies, hypersensitivity, or intolerance to the excipients of afuresertib (for excipient information, refer to the IB¹⁷).
9. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (eg, compromise well-being) or that could prevent, limit, or confound the protocol-specified assessments.
10. Any medical contraindication to the use of paclitaxel.
11. Prior radiotherapy ≤ 15 days prior to Study Day 1 (with the exception of a single fraction of radiotherapy for the purposes of palliation, which is permitted). In addition, patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis should also be excluded.
12. History of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, or torsade de pointes).
13. Prolonged corrected QT interval by the Fridericia's correction formula (QTcF) on the screening ECG > 470 msec. Receiving concomitant medications known to prolong QTc, or which are associated with torsade de pointes, and are unable to discontinue use while receiving study drug.
14. History or evidence for any of the following: severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including transient ischemic attacks) within 6 months prior to Study Day 1 or New York Heart Association Class III to IV heart disease.
15. Presence of uncontrolled hypertension (systolic blood pressure [BP] > 160 mmHg or diastolic BP > 100 mmHg). Patients with a history of hypertension are allowed, provided that BP is controlled to within these limits by anti-hypertensive treatment.
16. Human immunodeficiency virus (HIV)-positive patients with 1 or more of the following:
 - a. Not receiving highly active antiretroviral therapy
 - b. Receiving antiretroviral therapy that may interfere with the study drug (consult the Sponsor for review of medication prior to enrollment)
 - c. CD4 count < 350 based on a test within 3 months of the screening visit
 - d. An acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of the start of screening
17. Had a major non-abdominal surgery ≤ 30 days, or a major abdominal surgery within 8 weeks prior to first study treatment at Cycle 1 Day 1. In addition, patients who have anticipated major surgical procedures during the study, including but not limited to abdominal surgery (laparotomy or laparoscopy) prior to disease progression, such as colostomy or enterostomy reversal should also be excluded.
18. Presence of grade > 2 neuropathy.
19. Prior receipt of chemotherapy, PARP inhibitor, bevacizumab, or investigational therapy within 28 days of enrollment or within 5 half-lives of the agent, whichever is shorter.
20. Patients who are pregnant or lactating.
21. Patients with high risk of tuberculosis infection, based on investigator's clinical assessment, will be screened by tuberculosis screening test, such as the QuantiFERON[®]-TB Gold In-Tube test (QFT-GIT) or the T-SPOT[®].TB test (T-Spot).

22. Patients with active hepatitis B (positive hepatitis B surface antigen [hBsAg] test at screening) or hepatitis C (positive hepatitis C virus [HCV] antibody test at screening) are not allowed to be enrolled in this study. Note:
- Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative hBsAg test and a positive hepatitis B core antibody [hBcAb] test) are eligible.
 - Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
23. Patients with higher risk of gastrointestinal perforation/fistula, including but not limited to the following conditions:
- Presence of $\geq$ CTCAE Grade 2 weight loss over the 3 months prior to screening, or who had anorexia;
 - Evidence of direct bowel involvement with tumor: rectovaginal nodularity; CT evidence of direct bowel involvement;
 - Patients with serious non-healing wound or ulcer, with history of abdominal fistula or gastrointestinal perforation, or with intra-abdominal abscess within 28 days prior to screening.
 - Patients with prior history of gastrointestinal disease or pre-existing GI symptoms, such as diarrhea or vomiting $\geq$ grade 2, GI obstruction, GERD, inflammatory bowel disease, diverticular disease, etc. The presence of abdominal pain should be further evaluated for risk of GI perforation.

5.1.4 End of the Study

The end of the study is defined as 105 patients died for any reason, at that time a final analysis including all data would be performed.

5.1.5 Treatment After the End of the Study

Patients will receive standard of care treatment as determined by their healthcare provider after completion of their treatment in the study. Patients who, at the investigator's discretion, are deriving benefit at the time of study conclusion may be transferred to an afuresertib continuation therapy.

5.1.6 Screen and Baseline Failures

Patients who undergo screening or baseline assessments but do not receive study drug will be recorded in a screening log, along with the reason the patient was not enrolled or did not receive study drug.

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Studies publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. Screen failures can be rescreened once.

6 STUDY TREATMENTS

The term “study treatment” is used throughout the protocol to describe any products received by the patient as per the protocol design.

6.1 Afuresertib

6.1.1 Dosage and Administration

Product name	Afuresertib	
Formulation description	Each afuresertib 50 mg tablet, intended for oral administration, contains afuresertib (hydrochloride salt) equivalent to 50 mg of afuresertib (free base). Each afuresertib 75 mg tablet, intended for oral administration, contains afuresertib (hydrochloride salt) equivalent to 75 mg of afuresertib (free base).	
Dosage form	Tablet	
Unit dose strength(s)/Dosage level(s)	50 mg	75 mg
Physical description	A white round bi-convex tablet with no external markings	A white oval capsule-shaped tablet with no external markings
Route/ Administration/ Duration	Oral. The initial regimen will be QD dosing continuously.	
Dosing instructions	Dose with approximately 200 mL of water. Patients will be expected to fast overnight (ie, at least 8 hours) before dosing on PK sampling days. Patients should also fast for 2 hours after dosing. On days in which PK samples are not collected, patients may eat at any time with respect to ingestion of the drug unless fasting is required for laboratory tests. If a patient vomits after taking study drug, the patient should be instructed not to retake the dose and should take the next scheduled dose.	

- Arm 1: When used as the combination therapy of afuresertib plus weekly paclitaxel, 3 weeks is a cycle. The dose of afuresertib will be 125 mg PO daily and the dose of paclitaxel will be 80 mg/m² infused weekly on Day 1, Day 8, and Day 15 of each cycle. Treatment will continue until disease progression, death, unacceptable toxicity, or withdrawal of consent. On days when it is given with paclitaxel, afuresertib should be taken prior to initiation of paclitaxel infusion.
- Arm 2: Paclitaxel 80 mg/m² IV infusion on Days 1, 8, and 15 of a 3-week cycle. Treatment will continue until disease progression, death, unacceptable toxicity, or withdrawal of consent.

6.1.2 Packaging and Labeling

The tablets are packaged in white high-density polyethylene (HDPE) bottles with white plastic, induction-seal, child-resistant caps. The tablet bottles may contain desiccant. The recommended storage conditions, and expiry date where required, are stated on the product label. The contents

of the label will be in accordance with all applicable regulatory requirements. Laekna Limited will provide afuresertib tablets.

6.1.3 Preparation, Handling and Storage

No special preparation of afuresertib is required. Afuresertib is to be stored between 10 degrees and 30 degrees Celsius in the provided bottle. Maintenance of a temperature log (manual or automated) is required. Afuresertib must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of afuresertib must be limited to the investigator and authorized site staff. Afuresertib must be dispensed or administered only to patients enrolled in the study and in accordance with the protocol.

6.2 Paclitaxel

6.2.1 Dosage and Administration

Paclitaxel should be administered as a 1-hour IV infusion. The infusion rate may be decreased if needed to decrease the severity/frequency of hypersensitivity reactions. Frequent vital sign monitoring is required. Administration of concomitant medications to prevent/treat hypersensitivity reactions should follow local medical practice and the recommendations included in the product label.

6.2.2 Packaging and Labeling

Commercially available paclitaxel for IV administration will be obtained through the local pharmacy when possible and will be supplied in the commercial package with the required regulatory information. In those countries/sites where paclitaxel is not available locally, it will be sourced via a third-party vendor and supplied in the commercial package with required regulatory information. Investigators are responsible for ensuring that patients receive supplies of paclitaxel for the entire duration of the study, except in countries where regulatory authorities mandate that the Sponsor must supply all study treatment(s) required for study participation. The contents of the label will be in accordance with all applicable regulatory requirements.

6.2.3 Preparation, Handling and Storage

Follow the manufacturer's directions supplied with the product. The recommended storage conditions and expiry date for paclitaxel for IV infusion are stated on the product label. Paclitaxel must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of paclitaxel must be limited to the investigator and authorized site staff. Paclitaxel must be dispensed or administered only to patients enrolled in the study and in accordance with the protocol.

6.3 Treatment Assignment

Patients will be identified by a unique patient number that will remain consistent for the duration of the study.

Patients can be randomized remotely to be assigned to the treatment arm using an interactive

web response system (IWRS) upto 96 hours prior to Day 1. 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 vs. 3-5 prior platinum regimens). Upon completion of all the required screening assessments, eligible patients will be assigned to treatment with afuresertib plus paclitaxel (Arm 1) or paclitaxel (Arm 2) based on the respective stratification factors.

From the combination treatment arm, serial PK samples on Cycle 1 Day 1 and Cycle 2 Day 1 will be collected from approximately 20 patients. From the paclitaxel treatment arm, serial PK samples on Cycle 2 Day 1 will be collected from approximately 10 patients. From the beginning of the study, all patients who consent to participate in the serial PK sampling will be consecutively enrolled into the PK sampling population until approximately 20 patients in Arm 1 and 10 patients in Arm 2 have provided serial PK samples (see [Section 8.4.1](#) for further details).

6.4 Blinding

This is an open-label study.

6.5 Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product (IP) and paclitaxel dispensed and/or administered to study patients, the amount returned by study patients, and the amount received from and returned to Laekna Limited or its designee or destroyed by the study site, when applicable. Product accountability records must be maintained throughout the course of the study.

6.6 Treatment Compliance

Compliance with study treatment will be assessed through querying the patient during the site visit as well as a patient diary, and documented in the source documents and Case Report Form (CRF). A record of the number of afuresertib tablets dispensed to and taken by each patient must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

When patients are dosed at the study site, they will receive study treatments directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and electronic Case Report Form (eCRF). At-home dosing will be recorded in a patient diary.

The doses of study treatment and study participant identification will be confirmed at the time of dosing at the study site by a member of the study site staff other than the person administering the study treatment.

Paclitaxel will be intravenously administered to patients at the study site. Administration will be documented in the source documents and reported in the eCRF.

6.7 Patient Discontinuation

Patients will be withdrawn from the study treatment if any of the following occurs:

- Inter-current illness that prevents further administration of study drug. AE that is considered by the investigator or a Study Medical Monitor to warrant permanent discontinuation of study drug.
- A clinically significant AE caused by the study drug(s) leading to an interruption of both study drugs for greater than 14 consecutive days. In such case, the investigator should consult the Study Medical Monitor to discuss the possibility of discontinuing treatment. If the investigator and a Study Medical Monitor conclude that continued treatment could benefit a patient who has a greater than a 14 consecutive days of treatment delay, then the patient will be allowed to continue therapy with the approval of the Study Medical Monitor.
- Patient withdraws consent for further treatment or data collection.
- Once a patient has permanently discontinued from study treatment, the patient is not allowed to be retreated. For a patient who is receiving paclitaxel and afuresertib combination therapy, if permanent discontinuation of paclitaxel treatment is warranted due to paclitaxel-related toxicity, the patient should continue to be treated with afuresertib monotherapy, until disease progression, intolerable toxicity, or any of the reasons for discontinuation discussed in this section. After permanent discontinuation of afuresertib due to afuresertib caused AEs, patients can receive paclitaxel in isolation and remain on study.
- Disease progression.
- Severe noncompliance with protocol as judged by the investigator and/or Sponsor.
- Patient becomes pregnant.

The reason for discontinuing treatment with study drug will be clearly documented in the patient's medical record and on the Study Conclusion eCRF page. If the patient withdraws from treatment due to safety reasons (even voluntarily), 'adverse event' or 'serious adverse event' will be recorded as the primary reason for permanent discontinuation on the eCRF and the corresponding AE or SAE was recorded in the eCRF.

All patients who discontinue study treatment for any reason (other than withdrawal of consent for further treatment and data collection) will have the safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in the protocol.

All patients who discontinue study treatment for a reason other than PD, death, or withdrawal of consent for further treatment and data collection will have the end-of-treatment (EOT) visit within 30 days (± 7 days) after the last dose. The patient will then have calendar-based tumor assessments and CA-125 assessments until PD, death, or the start of next systemic anticancer therapy or being lost to follow-up, and will have OS and PFS follow-up until death or being lost to follow-up.

Patients have the right to discontinue the study at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study at any time, though efforts should be made to retain patient in the study if there is no conflicting health and safety concerns. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Death
- Patient withdrawal of consent for further treatment or data collection
- Lost to follow-up
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

6.8 Dose Adjustment/Stopping Criteria

The severity of AEs will be graded utilizing the NCI-CTCAE v5.0.³⁵ The dose modification criteria in [Table 3](#) should provide guidance for, but not act as a replacement for, sound clinical judgment. The investigator should use clinical judgment to determine which study treatment may be contributing to the toxicity necessitating dose adjustment, and make the appropriate change for that drug. For example, if the patient experiences $ANC < 500/mm^3$ during a cycle of therapy and the investigator feels the neutropenia is due to paclitaxel but not afuresertib, then the investigator should modify the dose of paclitaxel; the dose of afuresertib does not have to be modified if the investigator feels it is not contributing to the toxicity. If neutropenia persists after reduction of the chemotherapeutic agent, the investigator should consider reduction of the dose of afuresertib.

A maximum of two dose level modifications for afuresertib are allowed during the study. There is no limit on dose modification of paclitaxel.

Table 3. Dose Modification Guidance

Toxicity	Grade or Value	Dose Modification Suggestions	
		Afuresertib	Paclitaxel
Platelets	$\geq 50,000/\mu l$ to $< 100,000/\mu l$	None	Hold treatment until platelet count is $\geq 100,000/\mu l$. Recommend repeat platelet count in 1 week if treatment held. Consider reduction in dose by at least 20%.
	$< 50,000/\mu l$	Hold treatment until platelet count is $\geq 100,000/\mu l$. Recommend repeat platelet count in 1 week if treatment held. Consider dose reduction to 125 mg D1-4, Q7D, if after dose reduction in chemotherapy component, nadir platelet count again decreases to $< 50,000/\mu L$.	Hold treatment until platelet count is $\geq 100,000/\mu l$. Recommend repeat platelet count in 1 week if treatment held. Consider reduction in dose by at least 20%.

Toxicity	Grade or Value	Dose Modification Suggestions	
		Afuresertib	Paclitaxel
ANC	$\geq 500/\text{mm}^3$ to $< 1500/\text{mm}^3$	None	Hold treatment until ANC is $\geq 1500/\text{mm}^3$. Recommend repeat ANC in 1 week if treatment held.
	$< 500/\text{mm}^3$	Hold treatment until ANC is $\geq 1500/\text{mm}^3$. Recommend repeat ANC in 1 week if treatment held. Consider 125 mg D1-4 Q7D if ANC $\geq 1500/\text{mm}^3$; then return to 125 mg QD if ANC $\geq 1500/\text{mm}^3$ for 1 week.	Hold treatment until ANC is $\geq 1500/\text{mm}^3$. Recommend repeat ANC in 1 week if treatment held. Consider reduction of dose by at least 20%.
Febrile neutropenia (ANC $< 1000/\text{mm}^3$ and a single temperature of $> 38.3^\circ\text{C}$ or a sustained temperature of $\geq 38^\circ\text{C}$ for more than one hour.))		Hold treatment If fever resolves in 5 days, consider 125 mg D1-4 Q7D if ANC $\geq 1500/\text{mm}^3$; then return to 125 mg QD (following ANC recommendations).	Hold treatment If fever resolves in 5 days, consider reduction of dose by 20% (following ANC recommendations).
Peripheral sensory neuropathy	Grade 1	None	None
	Grade 2	None	Hold treatment until toxicity resolves to baseline. Consider at least 20% dose reduction.
	Grade 3	None	Hold treatment until toxicity resolves to grade 1 or less. Consider discontinuation of paclitaxel.
	Grade 4	Withdraw patient from study.	Withdraw patient from study.
Hyperglycemia (see also Section 6.8.4)	Grade 1-2	None	None
	Grade 3	Hold treatment. If resolved to grade 1 in 14 days, consider 125 mg, D1-4 Q7D for 1 week, then return to 125 mg QD.	None
	Grade 4 or ketoacidosis	Withdraw patient from study.	Withdraw patient from study.

Toxicity	Grade or Value	Dose Modification Suggestions	
		Afuresertib	Paclitaxel
Anaphylaxis (acute hypersensitivity reactions)	Severe reactions defined as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria.	None unless afuresertib is the only study drug being taken by the patient. In that case, immediately discontinue treatment and do NOT rechallenge.	Immediately discontinue treatment and do NOT rechallenge.
Conduction disorder	Grade 1 and 2	None	None
	Grade ≥ 3	None	Immediately discontinue treatment and do NOT rechallenge. Provide supportive care as needed.
Fatigue or Skin rash	Grade 1	Consider dose reduction to 125 mg D1-4, Q7D. Consider to return to 125 mg QD if resolved to baseline.	None
	Grade ≥ 2	Hold treatment until resolved to grade 1.	None
	Grade ≥ 3	Hold treatment until resolved to grade 1.	Hold treatment until resolved to grade 2.
Diarrhea	Grade 1	Consider dose reduction to 125 mg D1-4, Q7D. Consider to return to 125 mg QD if resolved to baseline*.	Consider dose reduction to 50 mg/m ² , IV weekly. Consider to return to 80 mg/m ² , if resolved to baseline.
	Grade ≥ 2	Hold afuresertib until the AE reduces to grade 1; Then resume afuresertib 125 mg, D1-4, Q7D for 7-14 days; If tolerated well, return to 125 mg QD*. *Patient with grade 1 diarrhea can be considered to return to 125 mg QD if no other risk factors of GI perforation based on investigator's clinical assessment.	Hold paclitaxel until the AE reduces to grade 1; Then resume paclitaxel 50 mg/m ² , IV weekly for 1-2 weeks; If tolerated well, return to 80 mg/m ² .

Toxicity	Grade or Value	Dose Modification Suggestions	
		Afuresertib	Paclitaxel
Other grade ≥ 3 non-hematological toxicity except rash (Section 6.8.3). See also details on grade 3-4 mucositis in Section 6.9.2.	Grade ≥ 3	Hold treatment. If resolved to baseline in 14 days, consider 125 mg D1-4, Q7D for 1 week. Consider to return to 125 mg QD in next cycle if no recurrence or new toxicities.	Hold treatment. If resolved to baseline in <14 days, consider dose reduction of 20%. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.

ANC = Absolute neutrophil count

Hematology laboratory tests in the afuresertib plus paclitaxel arm or paclitaxel alone arm on Days 8 and 15 of Cycle 1 and 2 will provide nadir counts.

6.8.1 Liver Chemistry Stopping Criteria

Liver chemistry stopping and follow-up criteria have been designed to assure patient safety and evaluate liver event etiology in consideration of the FDA Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation (2009).³⁶

The liver chemistry stopping criteria 1-5 are defined as follows:

1. ALT or AST $\geq 3 \times$ ULN **and total** bilirubin $\geq 2 \times$ ULN (alternatively, ALT or AST $\geq 3 \times$ ULN and international normalized ratio (INR) > 1.5 , if INR measured)

NOTE: If serum bilirubin fractionation is not immediately available, and if ALT or AST $\geq 3 \times$ ULN **and total** bilirubin $\geq 2 \times$ ULN, discontinue patient from study treatment. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT or AST $\geq 5 \times$ ULN
3. ALT or AST $\geq 3 \times$ ULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia)
4. ALT or AST $\geq 3 \times$ ULN persists for 4 weeks
5. ALT or AST $\geq 3 \times$ ULN and cannot be monitored weekly for 4 weeks

When any of the liver chemistry stopping criteria 1 – 5 are met, do the following:

- Immediately discontinue patient from study treatment
- Report the event to Laekna Limited or its designee **within 24 hours** of learning its occurrence
- Complete the SAE data collection tool if the event also meets the criteria for an SAE

- All events of ALT or AST $\geq 3 \times$ ULN **and** total bilirubin $\geq 2 \times$ ULN (alternatively, ALT or AST $\geq 3 \times$ ULN and INR > 1.5 , if INR measured; INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed ‘Hy’s Law’, **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**
- Perform follow-up assessments, and monitor the patient until liver chemistries resolve, stabilize, or return to baseline values, as described below
- Withdraw the patient from the study after completion of the liver chemistry monitoring (unless further safety follow-up is required or Lakena Limited approval of drug restart is granted, as described in [Section 6.8.1.2](#) and [Section 6.8.1.3](#)).
 - Follow-up for OS or progression is required following discontinuation from study treatment
- Do not restart IP unless written approval is granted by Lakena Limited ([Section 6.8.1.2](#) and [Section 6.8.1.3](#)), whereupon the patient continues in the study after completion of the liver chemistry monitoring ([Section 6.8.1.1](#))
- Patients meeting liver stopping criterion 5 should be monitored as frequently as possible

In addition, for patients meeting liver stopping criterion 1:

- Make every reasonable attempt to have patients return to clinic **within 24 hours** for repeat liver chemistries, liver event follow-up assessments ([Section 6.8.1.1](#)), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor patients twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

For patients meeting any of the liver stopping criteria 2 – 5:

- Make every reasonable attempt to have patients return to clinic **within 24-72 hours** for repeat liver chemistries and liver event follow-up assessments ([Section 6.8.1.1](#))
- Monitor patients weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values
 - Patients meeting liver stopping criterion 5 should be monitored as frequently as possible

6.8.1.1 Liver Event Follow-up Assessments

For patients meeting any of the liver chemistry stopping criteria 1 – 5, make every attempt to carry out the **liver event follow-up assessments** described below:

- Viral hepatitis serology including:
 - Hepatitis A immunoglobulin M (IgM) antibody
 - Hepatitis B surface antigen and hepatitis B Core Antibody (IgM)
 - Hepatitis C ribonucleic acid (RNA)

- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
- Hepatitis E IgM antibody
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
- Fractionate bilirubin, if total bilirubin $\geq 2 \times$ ULN
- Obtain CBC with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE form
- Record use of concomitant medications such as acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form
- Record alcohol use on the liver event alcohol intake form

The following assessments are required for patients with ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins)
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease
- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by high performance liquid chromatography [HPLC] assay more than 1 week following acetaminophen use)
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B deoxyribonucleic acid (DNA) and hepatitis delta antibody

NOTE: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed), as outlined in Le Gal et al.³⁷

6.8.1.2 Drug Restart/Rechallenge Following Liver Events that are Possibly Related to Investigational Product (IP)

Approval for drug restart by Laekna Limited, or its designee after agreement by Laekna Limited, can be considered if:

- The patient is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approval of drug restart/rechallenge must be obtained, as required.

- Study drug must be administered at the dose specified by Laekna Limited or its designee.
- Patients approved by Laekna Limited or its designee for restart/rechallenge of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

6.8.1.3 Drug Restart Following Transient Resolving Liver Events Not Related to IP

Approval for drug restart by Laekna Limited, or its designee after agreement by Laekna Limited, can be considered if:

- Liver chemistries have a clear underlying cause (eg, biliary obstruction, hypotension and liver chemistries have improved to normal or are within $1.5 \times$ baseline and ALT or AST $< 3 \times$ ULN). IEC or IRB approval of drug restart/rechallenge must be obtained, as required.
- Study drug must be administered at the dose specified by Laekna Limited or its designee.
- Patients approved by Laekna Limited or its designee for restarting IP must return to the clinic once a week for liver chemistry tests until stable, liver chemistries have been demonstrated, and then laboratory monitoring may resume as per protocol. If protocol-defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

6.8.2 QTcF Withdrawal Criteria

A patient that meets the criteria below will have study treatment permanently discontinued. The QT correction formula used to determine discontinuation should be the same one used throughout the study:

- QTcF > 500 msec or uncorrected QT > 600 msec
- Increase in QTcF > 60 msec from baseline
- If patient has underlying bundle branch block, then the QTcF withdrawal criteria depends on the baseline value:

Baseline QTcF value (with underlying bundle branch block)	QTcF withdrawal criteria
< 450 msec	> 500 msec
450-470 msec	> 530 msec

Withdrawal decisions are to be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTcF values of the 3 ECGs to determine whether the patient should be discontinued from the study.

6.8.3 Rash Dose Modification Criteria and Supportive Care Recommendations

Patients should contact the investigator immediately upon onset of a rash. Full supportive care should be provided to patients who experience a rash while on study. *Information contained in this section is a guideline. The investigator's best medical judgment should determine medical intervention for rash.*

Grade 1 rash (10% of body surface area, asymptomatic) or pruritus (localize without rash):

Consider afuresertib dose reduction from 125 mg QD to 125 mg D1-4, Q7D. Monitor for change in severity until signs and symptoms of rash are considered stable. Consider use of topical steroid (eg, hydrocortisone 1% or 2.5% cream). Hypoallergenic moisturizers and emollients for dry skin (5-10% urea in cetomacrogel cream or soft paraffin) may provide symptomatic relief for pruritus. Consider to return afuresertib dose to 125 mg QD if rash resolves to baseline.

Grade 2 rash (10-30% of body surface area, symptomatic):

Consider temporary discontinuation of afuresertib until rash resolves to grade 1. Monitor for change in severity until signs and symptoms of rash are considered stable. Provide appropriate supportive care for symptoms, including topical steroids (eg, hydrocortisone 2.5% cream) and antihistamines. Hypoallergenic moisturizers and emollients for dry skin (5-10% urea in cetomacrogel cream or soft paraffin) may provide symptomatic relief for pruritus. If rash symptoms persist two weeks or more, consider a short course of systemic steroids. Consider referral to a dermatologist and skin biopsy.

Grade 3-4 rash ($\geq 30\%$ of body surface area, symptomatic):

Contact the patient (by phone or in clinic) until signs and symptoms of rash are considered stable. Provide appropriate supportive care for symptoms, including topical steroids (eg, hydrocortisone 2.5% cream), a short course of systemic steroids, and antihistamines. Hypoallergenic moisturizers and emollients for dry skin (5-10% urea in cetomacrogel cream or soft paraffin) may provide symptomatic relief for pruritus. Refer patient to a dermatologist for consultation and skin biopsy. Consider temporary discontinuation of both study drugs until rash resolves to grade 1 (for afuresertib) or grade 2 (for paclitaxel), if systemic steroids do not provide symptomatic relief.

6.8.4 Hyperglycemia Dose Modification Criteria and Supportive Care Guidelines

Patients with clinically significant glucose elevation, with or without ketoacidosis, should be aggressively managed according to standardized guidelines developed for glucocorticoid-induced diabetes.³⁸ Study sites with a protocol/guideline for management of hyperglycemia should include a copy in the study document file. Early consultation with a diabetic specialist is also encouraged, especially for study participants with a history of diabetes.

If significant hyperglycemia (eg, fasting glucose ≥ 200 mg/dL) persists despite treatment and after stopping systemic glucocorticoids (where applicable), or in the event of life-threatening

complications, dose modification of afuresertib should also be considered, after discussion with a Laekna Limited or Clinical Research Organization (CRO) Medical Monitor. Dose modification of afuresertib should not be performed for asymptomatic hyperglycemia, or hyperglycemia that responds to other interventions.

6.9 Supportive Care

6.9.1 Diarrhea

Early diarrhea management for patients taking afuresertib is critical and must be initiated as soon as the first episode of diarrhea has occurred. At the time of starting afuresertib, the investigator should consider giving all patients a prescription for loperamide or analog, and be advised to keep the prescription with them at all times. The patient should be clearly instructed to start loperamide promptly after the first episode of diarrhea. A dose of 4 mg loperamide should be given after the first episode of diarrhea, and 2 mg every 4 hours or after every episode of unformed stool, until the patient is free from diarrhea for 12 hours. The maximum allowed daily dose of loperamide is 16 mg. The patient should contact the investigator as soon as possible after diarrhea starts, but should not delay loperamide dosing.

These following recommendations are intended to proactively manage the diarrheal symptoms in an effort to avoid more serious complications, and are based on published guidelines.³⁹ Guidelines such as these should never replace sound clinical judgment. These general management principles do not address comprehensive management of more serious or protracted diarrhea syndromes.

Recommended management of uncomplicated grade 1-2 diarrhea:

- Stop all lactose-containing products
- Drink 8-10 large glasses of clear liquids a day
- Eat frequent small meals
- Modify doses of study drugs per Table 3 “Dose Modification Guidance”
 - For grade 1 diarrhea, consider afuresertib dose reduction from 125 mg QD to 125 mg D1-4, Q7D and paclitaxel from 80 mg/m² to 50 mg/m² weekly. Consider to return to study specified doses if diarrhea resolves to baseline*.
 - For grade ≥ 2 diarrhea, temporarily hold afuresertib and paclitaxel until diarrhea resolves to grade 1. Then resume afuresertib 125 mg, D1-4, Q7D for 7-14 days and paclitaxel 50 mg/m², IV weekly for 1-2 weeks. If tolerated well, return to study specified doses*.

*Patient with grade 1 diarrhea can be considered to return to 125 mg QD if no other risk factors of GI perforation based on investigator’s clinical assessment.

- Administer loperamide as outlined above

Recommended management of grade 3-4 diarrhea:

- IV fluid hydration as appropriate

- Consider hospital admission
- Prophylactic antibiotics as needed (eg, fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is a fever or grade 3-4 neutropenia
- Temporarily discontinue both study drugs until diarrhea resolves to grade 1 (for afuresertib) or grade 2 (for paclitaxel) and discuss with Laekna Limited or CRO Medical Monitor

6.9.2 Mucositis

Mucositis is a frequent AE in patients treated with AKT inhibitors. The factors that possibly contribute to mucositis are decreased secretions from salivary glands and the interference of AKT inhibition with mucosal renewal. The breakdown of mucosal barrier predisposes the patient to bacterial, fungal (most commonly *Candida albicans*) and viral superinfections. In rare and extreme cases, the pain may prevent patients from taking adequate amounts of fluids and food, and thus patients may require parenteral nutrition.

In order to prevent oral mucositis, we recommend that patients on afuresertib are instructed about basics of oral care, which includes using soft toothbrush, rinsing and cleaning the oral cavity with water after every meal, and removal of dentures at the first sign of oral pain or inflammation.

The preventive measures for lower GI tract mucositis include maintaining adequate hydration, consideration of transient lactose intolerance, and reducing dairy intake.

Recommended management of uncomplicated grade 1-2 mucositis:

- Limit the diet to foods that do not require significant chewing; consider soft foods; acidic, salty, dry foods should be avoided
- Remove dentures
- Hold afuresertib for grade 2 mucositis
- Maintain adequate hydration
- In case of intraoral vesicles or unusually painful ulcerative lesions, consider swab for viral cultures and start empirical antiviral treatment with acyclovir or valacyclovir
- If patient develops oral candidiasis, topical treatment with nystatin solution or clotrimazole is recommended
- Administer topical analgesics (2% lidocaine solution, or other), or consider oral coating agents for pain control

Recommended management of grade 3-4 mucositis:

- Consider hospital admission
- IV fluid hydration and nutrition as appropriate
- Monitor electrolyte imbalance

- Provide adequate analgesia
- Administer ranitidine or omeprazole in case of epigastric pain
- If infection is suspected: consider antibiotics/antiviral/antifungal agents as needed, especially if mucositis is accompanied by oral thrush or vesicles, and/or grade 3-4 neutropenia
- Hold afuresertib and discuss with a Laekna Limited or CRO Medical Monitor

6.9.3 Dyspepsia

Based on nonclinical data and increasing clinical experience, it is possible that afuresertib may be a direct GI mucosal irritant such that patients with GI dysmotility or gastroesophageal reflux disease (GERD) may be predisposed to symptoms of dyspepsia. Therefore, if a patient experiences symptoms of grade 1-2 dyspepsia, the investigator should consider the following recommendations.

- A meal may be taken with afuresertib to ameliorate GI symptoms
- If possible, take each afuresertib capsule approximately 5 minutes apart with divided amounts of fluid (4-8 oz with each capsule for a total of at least 12 oz)
- Remain upright for 30 min after taking the last capsule of afuresertib
- In more severe cases, consider sucralfate and/or Gaviscon as supportive care to be taken at least 2 hours after ingestion of the last capsule of afuresertib, so as to avoid any potential drug-drug interactions

If the recommendations above are not sufficient to resolve the symptoms, the investigator should consider additional tests such as upper endoscopy or barium radiography.

7 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Patients will be instructed to inform the investigator prior to starting any new medications from the time of screening until the end of the study (Final Study Visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. The minimum requirement is that the drug name, route of administration, dose and frequency of dosing, along with start and stop dates of administration, should be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

7.1 Permitted Medications and Non-Drug Therapies

Patients should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

Paracetamol or acetaminophen, at the label-recommended dose, is permitted. Medications that contain paracetamol or acetaminophen should be counted in label-recommended dose. Other concomitant medication may be considered on a case-by-case basis by the Laekna Limited or CRO Medical Monitor.

Concurrent treatment with bisphosphonates is permitted. Prophylactic use of bisphosphonates in patients without metastatic bone disease is not permitted, except for the treatment of osteoporosis.

Anticoagulants are permitted only if the patient meets partial thromboplastin time (PTT) and INR entry criteria. Their use must be monitored in accordance with local institutional practice.

7.2 Prohibited Medications and Non-Drug Therapies

Patients should not receive anticancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormone therapy other than for replacement, surgery, and/or tumor embolization) directed towards the tumor for which they have been enrolled on the trial while on treatment in this study; although palliative radiation to control pain may be used following discussion with the Laekna Limited or CRO Medical Monitor.

Patients should not receive any other investigational drugs within 28 days or 5 half-lives, whichever is shorter, preceding the first dose of any of the drugs in the combination regimen.

Patients should abstain from taking any herbal and dietary supplements within 5 half-lives (or 14 days if the drug is a potential enzyme inducer) prior to study drug(s) dosing and until completion of the follow-up visit, unless there is little concern for a potential drug-drug interaction with the study drug(s). These herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. The investigator should contact the Laekna Limited or CRO Medical Monitor before initiating study treatment in a patient taking any herbal preparation.

Short (≤ 2 weeks) courses of oral corticosteroids intended to treat study treatment-related rash is allowed.

In addition, in vitro data indicate that afuresertib has the potential of being a perpetrator in drug-drug interactions through enzyme inhibition (with substrates of CYP3A4 and 2C8, IC₅₀ estimates of 3.7 to 6.0 µM [1.6 to 2.6 µg/mL] and 6.3 µM [2.7 µg/mL], respectively) and transporter inhibition (with substrates of OATP1B1 and BCRP, IC₅₀ estimates of 1.7 µM [0.7 µg/mL] and 2.9 µM [1.2 µg/mL]). Co-administration of afuresertib and medications that are a sensitive substrate of CYP3A4, OATP1B1, or BCRP with low therapeutic index **will be prohibited** (Table 4). Additional prohibited therapies with drugs that are known inhibitors or inducers of CYP3A are listed in Appendix 2.

Table 4. Drugs Potentially Affected by Afuresertib Resulting in Increased Exposure of These Substrates (PROHIBITED)

Generic Drug Name	Drug Class
CYP3A Substrates	
Carbamazepine	Anticonvulsants
Ergotamine, dihydroergotamine	Antimigraine
Clarithromycin	Antimicrobials
Pimozide	Antipsychotics
Amprenavir, atazanavir, indinavir, lopinavir, ritonavir, saquinavir	Antivirals
Amiodarone, disopyramide, quinidine, bosentan	Cardiovascular agents
Cyclosporine, everolimus, sirolimus, tacrolimus	Immunosuppressive agents
OATP1B1 Substrates	
Caspofugin	Antifungal
Atrasentan, methotrexate	Anticancer
BCRP Substrates	
Topotecan	Anticancer

CYP = Cytochrome P450

7.3 Cautionary Medications

7.3.1 Drugs Potentially Affected by Afuresertib (Afuresertib Perpetrator Interaction Potential)

Co-administration of afuresertib and medications that are a sensitive substrate of CYP3A4, OATP1B1, and BCRP but without low therapeutic index **will be used with caution** (Table 5).

Based on in vitro information, co-administration of afuresertib and medications that are a sensitive substrate of CYP2C8 without low therapeutic index **will be used with caution** (Table 5).

Table 5. Drugs Potentially Affected by Afuresertib Resulting in Increased Exposure of These Substrates (USE WITH CAUTION)

Generic Drug Name	Drug Class
CYP3A Substrates	
Fentanyl	Analgesics
Alfentanil, ropivacaine	Anesthetics
Losartan	Angiotensin II inhibitors
Ethosuxamide, trimethadione	Anticonvulsants
Buspirone, roboxetine, sertraline, trazadone, Venlafaxine	Antidepressants and anxiolytics
Emadastine, loratadine	Antihistamines
Artemether, halofantrine, lumefantrine, quinine	Antimalarial
Erythromycin, clindamycin, rifabutin, rifampin	Antimicrobials
Eletriptan	Antimigraine
α -dihydroergocriptine, bromocriptine	Antiparkinsonians
Aripiprazole, bromperidol, clozapine, haloperidol, quetiapine	Antipsychotics
Oxybutynin, tolterodine	Antispasmodics
Oseltamivir, delavirdine, tipranavir, nelfinavir	Antivirals
Amlodipine, barnidipine, diltiazem, dofetilide, dronedarone, eplerenone, felodipine, nifedipine, pranidipine, propafenone, verapamil, vesnarinone	Cardiovascular agents
Sildenafil, tadalafil, vardenafil	Erectile dysfunction treatments
Aprepitant, lansoprazole	Gastrointestinal agents
Atorvastatin, lovastatin, simvastatin	HMG CoA reductase inhibitors
Alprazolam, chlordiazepoxide, diazepam, flunitrazepam, midazolam, propofol, triazolam, zolpidem, zopiclone	Hypnotics and sedatives
Pioglitazone, repaglinide, rosiglitazone	Hypoglycemic agents
Temsirolimus	Immunosuppressive agents
Tretinoin	Retinoids
CYP2C8 Substrates	
Pioglitazone, repaglinide, rosiglitazone	Hypoglycemic agents
OATP and/or BCRP Substrates	
Atorvastatin, cerivastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	HMG CoA reductase inhibitors ²
Glyburide, repaglinide	Hypoglycemic agents ¹

1. Please note some drugs may be listed more than once. This is due to the fact that they are substrates for both CYP and a transporter (eg, OATP1B1, BCRP).
2. If patients are on a high dose of an HMG CoA reductase inhibitor, dose reduction should be considered. Monitoring for toxicities (such as rhabdomyolysis) should be considered.

CYP = Cytochrome P450

7.3.2 Drugs That May Potentially Affect Afuresertib

The metabolism of afuresertib may be mediated by CYP isozymes, which may include CYP3A4 with possible contributions from CYP2D6 and CYP1A2 (overall turnover < 5% by CYPs). However, the relative contribution of the various pathways to the elimination of afuresertib is presently unknown. Afuresertib is a substrate of human P-gp and of murine Bcrp1. Substances that potently inhibit or induce these enzymes/transporters could potentially lead to much higher/lower exposure in patients and alterations in the pharmacologic effects of afuresertib. The following medications ([Table 6](#)) may alter afuresertib elimination and **should be administered with caution**.

In addition, as the solubility of afuresertib is higher at pH 3 and 4 compared to other pHs, drugs altering the gastric pH could possibly alter the absorption of afuresertib and **should be administered with caution**.

Table 6. Drugs Potentially Affecting Afuresertib Elimination Resulting in Increased or Decreased Afuresertib Exposure (USE WITH CAUTION)

Generic Drug Name	Drug Class
Drugs that may increase exposure of afuresertib (CYP1A2, 2D6 or 3A4 inhibitors)	
Quinidine	Antiarrhythmics
Fluvoxamine, fluoxetine, nefazodone, paroxetine	Antidepressants
Fluconazole, itraconazole, ketoconazole, terbinafine, voriconazole	Antifungals
Ciprofloxacin, clarithromycin, erythromycin, isoniazid, telithromycin, troleandomycin	Anti-infectives
Amprenavir, atazanavir, delaviridine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir	Antivirals
Drugs that may increase exposure of afuresertib (gastric pH-modifying agents)	
Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, cimetidine, famotidine, nizatidine, ranitidine	Gastrointestinal Agents
Drugs that may decrease exposure of afuresertib (CYP inducers and others)	
Efavirenz, nevirapine	Antivirals
All rifamycin class agents (eg, rifampicin, rifabutin, rifapentine)	Antibiotics
Carbamazepine, phenobarbital, phenytoin	Anticonvulsants
Cortisone (> 50 mg), hydrocortisone (> 40 mg), prednisone (> 10 mg), methylprednisolone (> 8 mg) and dexamethasone (> 1.5 mg)	Glucocorticoids ¹
Oxandrolone, tizanidine, gemfibrozil, diomagnite (and related silicate compounds)	Miscellaneous

1. Glucocorticoid conversions are provided in parentheses.

CYP = Cytochrome P450

7.3.3 Drug to be Used with Caution with Paclitaxel

Paclitaxel is a substrate for metabolism by CYP2C8 and CYP3A4, and transport by P-gp. Caution should be exercised when paclitaxel is concomitantly administered with known substrates, inhibitors, and inducers of CYP3A4 and CYP2C8. Table 7 contains a list of medications that could potentially lead to higher/lower paclitaxel exposure in patients if co-administered. This list is not meant to be inclusive. The product label should be consulted for details.

Please note, a number of the following medications are also included in the tables above in association with afuresertib. If a drug is prohibited due to afuresertib, it is not allowed.

Table 7. Drugs Potentially Leading to Higher/Lower Paclitaxel Exposure

Generic Drug Name	Drug Class
Drugs that may increase exposure of paclitaxel (CYP3A4 or 2C8 substrates or inhibitors)	
Buspirone, fluvoxamine	Antidepressants and anxiolytics
Itraconazole, ketoconazole	Antifungals
Clarithromycin, telithromycin,	Antimicrobials
Eletriptan	Antimigraine
Atazanavir, indinavir, nelfinavir, ritonavir, saquinavir	Antivirals
Felodipine	Cardiovascular agents
Sildenafil	Erectile dysfunction agents
Lovastatin, simvastatin	HMG CoA reductase inhibitors
Midazolam, triazolam	Hypnotics and sedatives
Repaglinide, rosiglitazone	Hypoglycemic agents
Gemfibrozil	Lipid-regulating medication
Drugs that may decrease exposure of paclitaxel (CYP inducers and others)	
Carbamazepine	Anticonvulsants
Rifampin	Antimicrobial

CYP = Cytochrome P450

7.4 Treatment of Study Treatment Overdose

Laekna Limited does not recommend specific treatment for an overdose of afuresertib. The investigator should refer to the appropriate package insert if there is concern for a paclitaxel overdose. The investigator should use clinical judgment to treat any overdose. Treatment should be based on signs and symptoms. Any AEs that occur as a result of an overdose should be reported to a Laekna Limited or CRO Medical Monitor and recorded in the CRF. The overdose itself is not necessarily considered an AE, but the symptoms resulting from the overdose are considered AEs.

8 STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the patient prior to any study-specific procedures or assessments. All screening and baseline evaluations must be completed prior to initiating study treatment; relevant data will be captured in the CRF; all other patient data will be recorded in source documents and captured in the CRF.

Refer to the Time and Events Table for the timing of all assessments ([Table 8](#)). Details on efficacy and safety assessments are presented in [Section 8.3](#) and [Section 8.2](#), respectively.

The timing and number of planned study assessments, including safety, PK, biomarker, or other assessments may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme.

Certain assessments throughout the study are calendar-based, starting from the first day of dosing (Day 1). Dose interruptions and missed or delayed clinic visits should not alter the assessment schedule for any subsequent cycle. Those assessments that meet these criteria are denoted in the Time and Events Table ([Table 8](#)). Those assessments not designated as calendar-based are generally linked to the administration of paclitaxel and should be coordinated with scheduling of those study drugs with the understanding that if administration of these study drugs is delayed by more than 14 days, then calendar-based timing should be considered.

Table 8. 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):

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)
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	

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)
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				
CA-125 ^{1,13}	X							Every 6 weeks × 30 weeks, then every 8 weeks ⁹			X ²⁰	

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)
12-lead ECG	X											
Randomization		X ²⁴										
Fingerstick blood glucose		At home during therapy (the frequency of the test will be decided by the investigator based on clinical judgement)										
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												
Concomitant medication	X	X ²²										
Adverse events	X	X ²³										

Notes:

1. 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.
2. 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.
3. 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 6.7](#).
4. This assessment to be completed every 2 weeks for the first 2 cycles, then once per cycle.
5. 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.
6. Height at screening only.
7. If within 96 hours of Day 1, this assessment does not need to be repeated on Day 1.
8. CBC to be tested every week for the first 2 cycles, then once per cycle (ie, once every 3 weeks).
9. These assessments are calendar-based.
10. Creatinine clearance calculated using the Cockcroft-Gault formula.
11. 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.
12. 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.
13. 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 [Section 4.1.1](#) 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 $1 \text{ hour} \pm 6 \text{ minutes}$. If the paclitaxel infusion time is prolonged ($> 1 \text{ hour} \pm 6 \text{ minutes}$) 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, $C_{\text{trough,SS}}$ 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) if recommended by study physician. 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).

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.

8.1 Demographic/Medical History Assessments

The following demographic parameters will be captured: date of birth, gender, race, and ethnicity. Medical, surgical, and treatment history, including date (month and year) of first diagnosis, histology, current sites of disease as well as alcohol and tobacco history, and family history, will be taken as part of the medical history and disease status. Cardiovascular medical history/risk factors will also be assessed at baseline.

Medical and medication history will be assessed as related to the eligibility criteria listed in [Section 5.1.2](#) and [Section 5.1.3](#). Details concerning concomitant medication will be recorded starting from screening through post-study follow-up. At a minimum, the drug name, route of administration, dose and frequency of dosing, and the reason for use, along with start and stop dates should be recorded.

8.2 Safety

The safety assessments include monitoring of AEs, clinical laboratory tests, vital signs, ECGs, physical examinations, and ECOG performance status. Planned time points for all safety assessments are listed in the Time and Events Table ([Table 8](#)). 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.

8.2.1 Adverse Events

The investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

8.2.1.1 Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

“Lack of efficacy” or “failure of expected pharmacological action” *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from “lack of efficacy” will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient’s condition.

8.2.1.2 Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

- a. Results in death
- b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but

do not constitute a substantial disruption.

- e. Results in a congenital anomaly/birth defect in the offspring of a patient who received study drug.
- f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Protocol-specific SAEs:

- All events of possible drug-induced liver injury with hyperbilirubinemia, defined as ALT or AST $\geq 3 \times$ ULN **and** total bilirubin $\geq 2 \times$ ULN (or ALT or AST $\geq 3 \times$ ULN and INR > 1.5 , if INR measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a patient meets the criterion of total bilirubin $2 \times$ ULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations > 1.5 suggest severe liver injury.

- Any new primary cancers

8.2.1.3 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology or clinical chemistry), or other safety assessments (eg, ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as an SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, are not to be reported as AEs or SAEs.

8.2.1.4 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (ie, disease progression or hospitalization due to disease progression) does not need to be reported as an SAE; however, if there is any doubt as to whether the event is solely due to disease progression, the event should be recorded as an SAE. Death due to disease under study is to be recorded on the Death CRF form. However, if the underlying disease (ie, progression) is greater than that which would normally be expected for the patient, or if the investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.

8.2.1.5 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. When applicable, AE and SAE should be assessed and graded based upon the NCI-CTCAE version 5.0.³⁵

8.2.1.6 Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.

The causality between adverse events and the investigational drug may be evaluated as:

- "Related", i.e., there is reasonable possibility, or
- "Unrelated", i.e., there is no reasonable possibility

The evaluation of relationship can be referred to the following criteria:

- Reasonable possibility: There are facts or evidences indicating the correlation between the investigational drug and AE, possibly based on but not limited to the following information:
 - The occurrence of the event is temporally related with the exposure of the investigational drug;
 - An known drug profile of the same pharmacological class of investigational drug may possibly result in such an event;
 - The event is relieved after the investigational drug is discontinued or its dose is reduced;
 - The event reoccurs if the investigational drug was reintroduced after having been stopped;
 - Biological potential;
- No reasonable possibility: There are no facts or evidences indicating that the investigational

drug is related with AE, possibly based on but not limited to the following information:

- The event may be attributed to concomitant medications;
- The event may be attributed to existing disease/ clinical condition;
- The event may be attributed to a non-investigational drug;
- The occurrence of the event is not associated with administration of the investigational drug rationally and temporally;
- The event is an expected reaction in the target disease and/or population;
- Dechallenge/Rechallenge is negative;

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to Laekna Limited or its designee. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to Laekna Limited or its designee.** The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

8.2.1.7 Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time that the patient consents to participate in the study until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs will be collected over the same time period as stated above for AEs. All SAEs will be reported to Laekna Limited or its designee within 24 hours, as indicated in [Section 8.2.1.8](#).

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and non-serious AEs of special interest will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up. At any time after 30 days the investigator may report any AE that they believe possibly related to study treatment.

All AEs should be followed up, and follow-up information are recorded in the source documents and eCRF. For any AE unresolved after the end of the study, the investigator will continue to follow up and record the information in the source documents. The sponsor retains the right to request additional information for any subject with ongoing AE/SAE at the end of the study, if judged necessary.

8.2.1.8 Prompt Reporting of SAEs and Other Events

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator Safety Review Committee (SRC) to Laekna Limited or its designee as described in the following table once the investigator determines the event meets the protocol

definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	Timeframe	Documents	Timeframe	Documents
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	2 weeks	Pregnancy notification form	2 weeks	Pregnancy follow-up form
Liver chemistry abnormalities:				
ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN (or ALT or AST $\geq 3 \times$ ULN and INR > 1.5 , if INR measured) ²	24 hours ¹	SAE data collection tool.	24 hours	Updated SAE data collection tool.
ALT or AST $\geq 5 \times$ ULN; ALT or AST $\geq 3 \times$ ULN with hepatitis or rash or $3 \times$ ULN ≥ 4 weeks	24 hours ¹	SAE data collection tool.	24 hours	Updated SAE data collection tool.
ALT or AST $\geq 3 \times$ ULN and $< 5 \times$ ULN and bilirubin $< 2 \times$ ULN	24 hours ¹	SAE data collection tool is not needed unless elevations persist for 4 weeks or patient cannot be monitored weekly for 4 weeks		

1. Laekna Limited or its designee to be notified at onset of liver chemistry elevations to discuss patient safety.
2. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.

8.2.1.9 Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to SRC and Laekna Limited or its designee is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

Laekna Limited or its designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Laekna Limited or its designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Laekna Limited policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (eg, summary or listing of SAEs) from Laekna Limited or its designee will file it with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

8.2.2 Pregnancy Testing, Prevention and Reporting

8.2.2.1 Pregnancy Test and Prevention

The need for a screening pregnancy test depends on whether a female patient is of childbearing potential or non-childbearing potential.

A female of non-childbearing potential (ie, physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy), or bilateral tubal ligation, or is post-menopausal. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile; eg, age appropriate, > 45 years in the absence of hormone replacement therapy (HRT). In questionable cases, the patient must have a follicle-stimulating hormone (FSH) value > 40 mIU/mL and an estradiol value < 40 pg/mL (< 140 pmol/L).

A female of childbearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

If a female patient is of childbearing potential, she must have a serum beta-human chorionic gonadotropin (β -HCG) pregnancy test performed within 14 days prior to the first dose of study treatment. Patients with a positive pregnancy test result must be excluded from the study. Patients with a negative pregnancy test result must agree to use an effective contraception method as described below during the study until 30 days following the last dose of study treatment or 6 months after the last dose of paclitaxel, whichever is longer.

Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female patient's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least 30 days after the last dose of study treatment.
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

8.2.2.2 Pregnancy Reporting

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure patient safety, each pregnancy must be reported to Laekna Limited or its designee within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy

complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the patient has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to Laekna Limited or its designee.

8.2.3 Physical Exams

Physical examination will include head, eyes, ears, nose, and throat, chest, cardiac, abdominal, extremities, neurologic, and lymph node examinations. At the time points indicated in [Table 8](#), body weight will be measured, and patients will be assessed for signs of fluid retention/edema.

8.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Status

The performance status assessment is based on the ECOG scale:⁴⁰

- 0 – Fully active, able to carry on all pre-disease performance without restriction.
- 1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
- 2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3 – Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
- 5 – Dead.

8.2.5 Vital Signs

Vital sign assessments at the time points indicated in [Table 8](#) will include BP, heart rate, respiratory rate, and oral, or axillary, or tympanic body temperature. 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.

8.2.6 Electrocardiogram (ECG)

ECG recording will be performed for screening purposes only. Repeat measurement will be at the discretion of the investigator, if clinically indicated.

At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after at least a five-minute rest with the patient in a semi-recumbent or supine position. Each assessment will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

All ECGs must include QTcF measurements. Those values greater than 470 msec as calculated by the machine must be confirmed manually using Fridericia's formula given below:

- The Fridericia's formula is: $QTcF = QT/(RR^{1/3})$
- If there are any clinically significant abnormalities, including but not limited to a $QTcF > 500$ msec, repeat the test with two additional ECGs taken at least 5 minutes apart.
- A single 12-lead ECG should be performed at screening.

8.2.7 Clinical Laboratory Assessments

Hematology, clinical chemistry, and additional parameters to be tested are listed in [Table 9](#):

Table 9. Clinical Laboratory Assessments

Category	Tests		
Hematology	• Platelet Count	• Hemoglobin	• WBC Count (absolute)
Automated WBC Differential	• Neutrophils • Lymphocytes	• Eosinophils • Monocytes	• Basophils
Coagulation	• PT	• INR	• PTT
Standard Clinical Chemistry	• BUN • Creatinine • Glucose, fasting • Sodium • Total Protein • Magnesium	• Potassium • Chloride • Total CO ₂ • Calcium • Albumin	• AST (SGOT) • ALT (SGPT) • Phosphorous • Alkaline phosphatase • Total and direct ¹ bilirubin
Additional Chemistry/Laboratory Assessments	• Fasting lipid panel • CA-125 ²	• TSH • Insulin	• HbA1C • 1,5-anhydroglucitol
Pregnancy Testing for Females	• Serum pregnancy testing at screening and then urine or serum during study		

ALT = Alanine transaminase; AST = Aspartate transaminase; BUN = Blood urea nitrogen; HbA1c = Hemoglobin A1c; INR = International normalized ratio; PT = Prothrombin time; PTT = Partial thromboplastin time; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase; TSH = Thyroid stimulating hormone; WBC = White blood cells

1. Direct bilirubin should be assessed only if total bilirubin is elevated beyond the ULN.
2. All CA-125 assessments will be performed by the central lab.

All screening tests will be performed by the central lab in the US, or local labs in China (except 1,5-anhydroglucitol, insulin and CA-125 tests in China, which will be performed by the central lab). All clinical laboratory tests (excluding CA-125), starting from C1D1, will be performed at laboratory facilities approved by the investigational site.

8.3 Efficacy

The detailed plan for radiographic tumor assessment schedule, CA-125 test schedule, and patient's survival follow-up are listed in the study schedule ([Table 8](#)).

Tumor response assessment by RECIST 1.1 will be evaluated during the trial for all randomized patients (Appendix 3). The investigator will perform the tumor assessment based on the study schedule. The primary efficacy endpoint of PFS will be based on the investigator's assessment ([Section 8.3.1](#)). However, radiographic imaging for tumor assessment will be collected and stored at a central vendor, a BICR (Blinded Independent Central Review) may take place at the end of trial to provide additional review for tumor response. The composition and responsibilities of the BICR Committee will be described in a separate charter.

8.3.1 Efficacy Endpoints

The primary efficacy endpoint of this study is 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.

The secondary efficacy endpoints of this study are:

- Overall survival (OS), defined as the time from randomization until death for any reason.
- Objective response rate (ORR), defined as the percentage of measurable disease participants with advanced or metastatic cancer who have achieved either complete response (CR) or partial response (PR) while receiving treatment in this clinical study.
- Duration of response (DOR), defined as time from first observation of response (CR or PR) until first observation of documented disease progression or death, whichever occurs first.
- Disease control rate (DCR), defined as the percentage of patients who have achieved CR, PR or stable disease to study treatment.
- CA-125 response, defined as complete CA-125 response, partial CA-125 response or progression of OC based on serum CA-125 levels, as described in [Section 8.3.5](#).

8.3.2 Baseline Documentation of Target and Non-target Lesions

- All baseline lesion assessments must be performed within 28 days of start of study treatment.
- Lymph nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with < 15 mm and but $\geq$ 10 mm short axis are considered non-measurable.
- Pathological lymph nodes with $\geq$ 15 mm short axis are considered measurable and can be selected as target lesions; however, lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of

their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by computed tomography (CT) or magnetic resonance imaging (MRI) can be considered measurable. Bone scans, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans, or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

8.3.3 Baseline Documentation of CA-125 Status

To be considered for response, the baseline CA-125 must be at least twice the upper limit of the reference range and evaluated within 14 days prior to starting treatment.

8.3.4 Efficacy Assessment by RECIST 1.1

Disease progression and response evaluations determined according to the definitions established in the RECIST 1.1.⁴¹

See the Time and Events Table ([Table 8](#)) for the schedule of efficacy assessments. Disease assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. 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.

The following are required at baseline: imaging appropriate to assess sites of disease and clinical disease assessment for palpable lesions. At each post-baseline assessment, evaluations of the sites of disease identified by these scans are required.

Confirmation of CR and PR will not be required in this protocol, as ORR is not the primary endpoint of this randomized, active-controlled clinical study.⁴¹

8.3.4.1 Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.

- All measurements should be taken and recorded in millimeters, using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- FDG-PET is generally not suitable for ongoing assessments of disease. However, FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion.
- If positron emission tomography (PET)/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/calipers to measure the size of the lesion, is required.⁴¹

CT and MRI: Contrast enhanced CT with 5 mm contiguous slices is recommended.

Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible, the same scanner should be used.⁴¹

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however, chest CT is preferred over chest X-ray.⁴¹

Brain Scan: If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

8.3.4.2 Assessment of Patient Completion

If the last radiographic assessment was more than 3 weeks prior to withdrawal from study and PD has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

8.3.4.3 Guidelines for Evaluation of Disease

8.3.4.3.1 *Measurable and Non-measurable Definitions*

Measurable lesion: A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- ≥ 10 mm with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, the minimum size of a measurable lesion

must be at least double the slice thickness (eg, if the slice thickness is 10 mm, a measurable lesion must be ≥ 20 mm).

- ≥ 10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥ 20 mm by chest X-ray.

Additionally, lymph nodes can be considered pathologically enlarged and measurable if

- ≥ 15 mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, only the short axis will be measured.⁴¹

Non-measurable lesion: All other lesions including lesions too small to be considered measurable (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm and < 15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.⁴¹

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-measurable only disease: The presence of only non-measurable lesions.

8.3.4.4 Response Criteria

8.3.4.4.1 *Evaluation of Target Lesions*

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be < 10 mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (eg, percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (eg, percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (eg, sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis < 10 mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (eg, 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

8.3.4.4.2 Evaluation of Non-target Lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (eg, < 10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline $\geq$ 10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

- Sites of non-target lesions, which are not assessed at a particular time point based on the assessment schedule, should be excluded from the response determination (eg, non-target response does not have to be "Not Evaluable").

8.3.4.4.3 New Lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

8.3.4.4.4 Evaluation of Overall Response

Table 10 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for patients with measurable disease at baseline.

Table 10. Evaluation of Overall Response for Patients with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete response, PR = Partial response, SD = Stable disease, PD = Progressive disease, NA= Not applicable, NE = Not evaluable.

8.3.4.4.5 Evaluation of Best Overall Response

The BOR is the best response recorded from the random assignment until disease progression/recurrence and will be determined programmatically by Laekna Limited (or designee) based on the investigator's assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose 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 not evaluable.

8.3.5 Efficacy Assessment by GCIG CA-125 Criteria

Circulating serum CA-125 will be evaluated for patients as detailed in Table 8. Correlations will be studied between the objective response of study drug treatment/disease progression and the changes of CA-125 levels and CA-125 level as secondary endpoints of the study.

Disease progression and response evaluations determined according to the definitions established by GCIG.⁴²

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.

8.3.5.1 Assessment of Patient Completion

If the last CA-125 assessment was more than 3 weeks prior to withdrawal from study and PD has not been documented, an assessment should be obtained at the time of withdrawal from study.

8.3.5.2 Response Criteria

A patient is categorized as a **partial CA-125 responder** if the CA-125 level has decreased by a minimum of 50%. The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response.

A patient is categorized as a **complete CA-125 responder** if the CA-125 level has decreased by a minimum of 50% AND normalized; ie, is within the reference range.

Patients who have a decrease in 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. All CA-125 responses must be confirmed and maintained for at least 28 days.

Progression is defined as below:

- Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of $CA-125 \geq 2 \times$ the upper limit of the reference range on 2 occasions at least 1 week apart **OR**

- Patients with elevated CA-125 pretreatment which never normalizes, must show evidence of $CA-125 \geq 2 \times$ nadir value on 2 occasions at least 1 week apart **OR**
- Patients with CA-125 in the reference range pretreatment must show evidence of $CA-125 \geq 2 \times$ upper limit of the reference range at least 1 week apart

Patient who progresses solely based on CA-125 values should continue to receive study treatment per protocol.

8.4 Pharmacokinetics

PK samples will be collected to characterize the PK of both the afuresertib plus paclitaxel and the paclitaxel alone arms. PK plasma samples from Arm 1 may also be used for exploratory metabolite analysis.

- Arm 1: first 20 patients who agree to participate in PK study and sign consent.
- Arm 2: first 10 patients who agree to participate in PK study and sign consent.

If a patient experiences an AE that fits the criteria of an SAE and if a relationship of the SAE to study drug treatment cannot be immediately ruled out, an unscheduled PK blood sample should be collected for measurement of plasma drug concentration, unless the event occurs at the same day of scheduled PK collection.

8.4.1 Blood Sample Collection for Pharmacokinetics of both Afuresertib Plus Paclitaxel and Paclitaxel Alone Arms

PK sampling time points for both study arms are detailed in [Table 8](#) and [Section 4.1.1](#).

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 $1 \text{ hour} \pm 6 \text{ minutes}$. If the paclitaxel infusion time is prolonged ($> 1 \text{ hour} \pm 6 \text{ minutes}$) due to infusion reaction, the 1-hour post-dose PK sample should be collected immediately at the end of the infusion.

The actual date and time of dosing and of each blood sample collection will be recorded. Approximate time of any meal consumed within 2 hours of any blood sample for PK on serial PK sampling days will be recorded. Planned sample collection times or study day may be revised based on newly available PK data (eg, to obtain data closer to the time of peak plasma concentration) to ensure appropriate monitoring. These changes must be approved and documented by Laekna Limited.

8.4.2 Pharmacokinetic Sample Analysis

Plasma analysis will be performed at a central laboratory authorized by the Sponsor. Concentrations of afuresertib and paclitaxel will be determined in plasma samples using the currently approved analytical methodology. Raw data will be stored at the central laboratory.

8.4.3 Meals and Dietary Restrictions

Patients may take afuresertib in either the fasted or fed state; ie, there is no requirement for fasting except on PK sampling days or when fasting is required for laboratory tests. On days where serial PK sampling is to be done, patients should fast overnight (ie, at least 8 hours) and should continue fasting until at least 2 hours after administration of the morning dose of afuresertib. Fasting will consist of avoiding the oral ingestion of calorie-containing products; however, ingestion of water is permitted. Patients will not be able to have any saltine crackers for GI upset on PK days. Requirements for fasting before and after dosing may be modified based on available PK, and safety data.

In addition, patients shall abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pomelos within 7 days prior to the first dose of afuresertib until the end of the study.

8.5 Biomarkers and Other Evaluations

8.5.1 1,5-Anhydroglucitol and Insulin

1,5-anhydroglucitol and insulin will be assessed as outlined in [Table 8](#).

8.5.2 Tumor Tissue Biomarkers

Patients will have tumor tissue (either biopsy samples or tumor tissue slides) collected for biomarker analysis. For patients who do not provide a tumor sample from previous archival tumor samples or from fresh tumor biopsy, the Sponsor should be consulted about their qualification to enter this study as reviewed on a case-by-case basis.

As an exploratory objective, a retrospective stratified analysis on anti-tumor efficacy by biomarker-positive status and biomarker-negative status for PI3K/AKT/PTEN pathway alterations will be performed, eg, alterations of PI3K/AKT/PTEN pathway determined by NGS and the level of phospho-AKT determined by IHC. The mutations of BRCA1 and BRCA2 will also be determined by NGS. The status of these biomarkers does not determine the patient's eligibility to be enrolled in this study. The relationships between alterations of tumor DNA, and/or the level of phospho-AKT, and the ORR, DOR, DCR, PFS, OS, and CA-125 response will be assessed.

9 DATA MANAGEMENT

For this study, patient data will be entered into eCRFs, transmitted electronically to a Laekna Limited-approved CRO and combined with data provided from other sources (eg, diary data) in a validated data system.

The Laekna Limited-approved CRO will identify and implement the most effective data acquisition and management strategy for each clinical trial protocol and deliver datasets which support the protocol objectives.

Management of clinical data will be performed in accordance with applicable CRO standards and data cleaning procedures to ensure the integrity of the data; eg, removing errors and inconsistencies in the data. Validated dictionaries will be used to code AEs and medical history (Medical Dictionary for Regulatory Activities [MedDRA] version 22.0 or above) and concomitant medications (World Health Organization [WHO] Drug Global version 2019 or above). eCRFs (including queries and audit trails) will be retained by the CRO, and copies will be sent to the investigator to maintain as the investigator copy.

In all cases, data collection will consider privacy laws in the applicable countries or regions.

10 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

10.1 Hypotheses

This study is designed to evaluate the clinical efficacy and safety of afuresertib (LAE002) administered in combination with paclitaxel versus paclitaxel alone in patients with PROC. The previous Phase I/II study (PKB116611) has reported preliminary efficacy in 28 patients with PROC evaluable for investigator-reported best response per RECIST 1.1: 9 patients achieved confirmed CR or PR (ORR: 32.1%, 95% CI: 15.9-52.4) and 15 patients achieved unconfirmed CR or PR (ORR: 53.6%, 95% CI: 33.9-72.5) with a median PFS of 7.1 months (95% CI: 6.3-9.0). Therefore, this Phase II study is aiming to provide further evidence of the efficacy and safety of afuresertib in managing the patients with PROC in a large sample size based on the results of the previous Phase I/II study.

The PFS according to RECIST v1.1 will be assessed as the primary endpoint in this Phase II Study LAE002INT2001. The previous Study PBK116611 has shown a PFS of 7.1 months to a different chemotherapy regimen of afuresertib plus paclitaxel (Q3W) plus carboplatin (Q3W).¹⁶ In this Phase II trial (LAE002INT2001), the study population treated with the combination therapy of afuresertib and weekly paclitaxel is expected to have an improved median PFS, i.e. 6.5 months, a slightly lower efficacy compared to the that of the above triple combination regimen.

The study will test the following hypotheses:

$$H_0: PFS_{\text{comb}} = PFS_{\text{ctrl}} \text{ versus } H_a: PFS_{\text{comb}} \neq PFS_{\text{ctrl}}.$$

10.2 Sample Size Determination

The primary endpoint of this study is PFS. Previous studies^{2,3,4} have shown that PROC patients have a median PFS of around 3.5 months with weekly paclitaxel after 1 to 5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed. The combination therapy is expected to result in an estimated 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.

10.3 Data Analysis Considerations

The primary data analysis 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 will be performed for OS only when the null hypothesis for the primary endpoint is rejected. The final OS analysis including all data will be conducted at the end of the study as defined in [Section 5.1.4](#).

10.3.1 Analysis Sets

All analysis sets will be identified prior to database lock.

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.

The **Safety Set** 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.

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.

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 (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.

10.3.2 Interim Analysis

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. Hypothesis testing of OS will be conducted if improvement of PFS demonstrates statistical significance (for more multiplicity handling, refer to [Section 10.3.3.2](#)).

10.3.3 Key Elements of Analysis Plan

Statistical analyses for the CSR and separated popPK analysis report will be the responsibility of the designated CRO(s).

Primary and secondary efficacy analyses are discussed in [Section 10.3.3.3](#). Safety analyses are discussed in [Section 10.3.3.4](#).

Data will be listed and summarized according to the Laekna Limited or designee reporting standards, where applicable. Complete details will be documented in the Statistical Analysis Plan (SAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the SAP and final CSR.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant PK measurements.

The reason for discontinuation from treatment and study will be summarized and listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each patient.

Other missing data will simply be noted as missing on appropriate tables/listings.

10.3.3.1 Patient Demographics and Other Baseline Characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for all patients in the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3.3.2 Treatments (Study Treatment, Concomitant Therapies, Compliance)

10.3.3.2.1 Study treatment

The actual dose and duration in days of study treatment, as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration) will be listed and summarized by means of descriptive statistics in the CSR. Categories for relative dose intensity of study drug will be specified as < 0.5 , $\geq 0.5 - < 0.75$, $\geq 0.75 - < 0.9$, $\geq 0.9 - < 1.1$ and ≥ 1.1 . The number and proportion of patients within each category will be presented by treatment. The Safety Set will be used.

10.3.3.2.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug treatment will be listed by patient and summarized by anatomical therapeutic chemical

(ATC) term by means of contingency tables. The FAS will be used.

10.3.3.2.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized.

Study medication compliance will be assessed by relative dose intensity and compliance of afuresertib.

10.3.3.3 Efficacy Analyses

10.3.3.3.1 Primary analysis

The primary endpoint of drug efficacy is PFS. The primary analysis of PFS will be based on tumor assessment results according to RECIST 1.1.

For each arm, PFS will be analyzed using the Kaplan-Meier method. The median PFS will be provided along with the 95% CI. The primary statistical analysis will be based on an unstratified log-rank test. The hazard ratio (HR) and 95% CI will be calculated based on an unstratified Cox proportional hazards model. PFS censoring rules will be specified in details in the SAP.

A sensitivity analysis may be performed using the BICR-reviewed tumor assessment results. These analyses on PFS will be performed for the FAS as primary analysis.

Additional sensitivity analyses for the primary endpoint PFS based on tumor assessments will be performed.

More detail on the statistical analyses will be provided in the statistical analysis plan (SAP).

10.3.3.3.2 Secondary analyses

Analysis of OS

OS will be analyzed using the Kaplan-Meier method. The median OS will be provided along with the 95% CI. The HR and 95% CI will be calculated based on an unstratified Cox proportional hazards model.

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.

Analysis of the other secondary endpoints

BOR according to RECIST 1.1 will be summarized.

The Clopper-Pearson method will be used to provide an estimation of ORR, DCR and CA-125 response rates with 95% CIs and the wald method will be used for treatment differences with 95% CIs for these endpoints.

DOR will be analyzed using the Kaplan-Meier method. The median DOR will be provided along with the 95% CI. The HR and 95% CI will be calculated based on an unstratified Cox proportional hazards model.

Further details of the statistical analysis methodology for all endpoints will be provided in a separate SAP.

10.3.3.4 Safety Analyses

10.3.3.4.1 Adverse events

All AEs recorded during the study will be summarized. The incidence of TEAEs (new or worsening from baseline) will be summarized by primary system organ class, severity based on the NCI-CTCAE v5.0, type of AE, and relationship to the study drug. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by primary system organ class and preferred term of AE. Any other information collected (eg, start/end dates and duration of AE, severity or relatedness to study medication) will be listed as appropriate.

10.3.3.4.2 Clinical laboratory evaluations

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using CTCAE v5.0. Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

For each laboratory test (eg, hematology, biochemistry, etc.), a listing of laboratory values will be provided by laboratory parameter, patient and treatment arm. Laboratory data will be summarized by presenting grade shift tables for those parameters for which CTCAE v5.0 allows classification. All remaining data will be summarized by presenting shift tables based on normal ranges.

10.3.3.4.3 Other safety measures

The results of scheduled assessments of body weight, vital signs, and 12-lead 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 (ie, no visit windows will be applied). All data will be listed. Further details will be provided in the SAP.

10.3.3.4.4 Tolerability

Tolerability of study drug will be assessed by summarizing the number of dose interruptions, dose reductions, and discontinuations from study drug due to AE. Reasons for dose interruption, dose reductions, and discontinuations from study drug due to AE will be listed by patient and summarized.

10.3.3.5 Pharmacokinetic Analyses

PK analysis will be the responsibility of Laekna Limited or designee. If serial PK samples are obtained, plasma afuresertib plus paclitaxel concentration-time data will be analyzed by non-compartmental methods with WinNonlin 8.0 or above. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the PK parameters detailed in [Section 3](#) will be determined. PK data will be presented in graphical and tabular form and if appropriate may be summarized descriptively. Individual plasma concentrations of afuresertib plus paclitaxel will be listed.

Further details will be provided in the SAP.

An exploratory PopPK analysis will be performed on the afuresertib data obtained in this study and, if data are not sufficient, using a meta-analysis approach combining data from previous studies or literature. These PK data, combined with data describing dose administration, timing of blood samples relative to dose administration, and information regarding intrinsic and extrinsic factors, will allow for the development of a PopPK model for afuresertib. This model will be used to characterize the PK of afuresertib and assess the potential impact of covariates (eg, demography, race, paclitaxel or other concomitant administrations, disease status) on variability in afuresertib PK. In addition, the PopPK model will be used to generate participant-specific estimates of afuresertib exposure on days where the PK was not assessed. Additional details of the PopPK model development and analysis will be provided in a separate PopPK analysis plan and results of the PopPK analysis will be reported separately from the CSR.

10.3.3.6 Predictive Biomarker Analyses

Subgroup analyses will be performed to evaluate the efficacy of afuresertib administered in combination with paclitaxel versus paclitaxel in patients with median/high phospho-AKT and/or PI3K/AKT/PTEN pathway alterations. The efficacy analysis methods in [Section 10.3.3.3](#) will be used as appropriate.

11 STUDY CONDUCT CONSIDERATIONS

11.1 Posting of Information on Publicly Available Clinical Trial Registries

Study information from this protocol will be posted on publicly available clinical trial registries before enrollment of patients begins.

11.2 Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, the approved Laekna Limited CRO will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable patient privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/IEC review and favorable opinion/approval of study protocol and any subsequent amendments.
- Patient informed consent.
- Investigator reporting requirements.

Laekna Limited will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each patient prior to participation in the study.

11.3 Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and Laekna Limited procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Laekna Limited requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

The investigator is responsible for the validity of all study data collected at the site.

The investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents and clinical study supplies, and to allocate their time and the time of their staff to the monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of patients are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11.4 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.

11.5 Study and Site Closure

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and Laekna Limited (or designee) Standard Operating Procedures.

Laekna Limited reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If Laekna Limited determines that such action is required, Laekna Limited will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Laekna Limited or its designee will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, Laekna Limited or its designee will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Laekna Limited or its designee will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

When the primary objective of this study is met, Laekna Limited reserves the right to terminate this study and may offer any patients still receiving study treatment the ability to enroll on a continuation (rollover) study provided they meet the eligibility criteria for the continuation trial.

11.6 Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to

be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (eg, for a Laekna Limited [or designee] audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

Laekna Limited will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, Laekna Limited standard operating procedures, and/or institutional requirements.

The investigator must notify Laekna Limited (preferably in writing) of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

11.7 Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Laekna Limited site or other mutually agreeable location.

Laekna Limited will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study patients, as appropriate.

Laekna Limited aims to post a results summary to <http://www.ClinicalTrials.gov> and other publicly available registers no later than 12 months after the last patient's last visit (LPLV). In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LPLV. Laekna Limited also aims to publish the full study protocol on the Laekna Limited Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the Laekna Limited Clinical Study Register to supplement the results summary.

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13 APPENDICES

Appendix 1: Cockcroft-Gault Formula

$CL_{cr}(\text{mL/min}) = \frac{Q \times (140 - \text{age}[\text{yr}]) \times \text{actual body weight} [\text{kg}]}{(72 \times \text{serum creatinine} [\text{mg/dL}])}$ Q = 0.85 for females Q = 1.0 for males

Source: Devine BJ. Gentamicin therapy. Drug Intell Clin Pharm 1974;8:650–5.

Appendix 2: Prohibited Medications/Therapy**Examples of clinical substrates:**

CYP enzymes	Sensitive substrates	Moderate sensitive substrates
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil; budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil

Examples of clinical inducers:

CYP Enzymes	Strong Inducers	Moderate Inducers	Weak Inducers
CYP3A	carbamazepine ^(a) , enzalutamide ^(b) , mitotane, phenytoin ^(c) , rifampin ^(d) , St. John's wort ^(e)	bosentan, efavirenz, etravirine, modafinil	

(a) Strong inducer of CYP2B6, CYP3A, and moderate inducer of CYP2C9.

(b) Strong inducer of CYP3A and moderate inducer of CYP2C9, CYP2C19, CYP3A.

(c) Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9.

(d) Strong inducer of CYP3A and moderate inducer of CYP1A2, CYP2C19.

(e) The effect of St. John's wort varies widely and is preparation-dependent.

CYP = Cytochrome P450

Appendix 3: Response Evaluation Criteria in Solid Tumors 1.1**Table 1 – Time point response: patients with target (+/- non-target) disease.**

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD ^a
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

^a a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR ^a
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

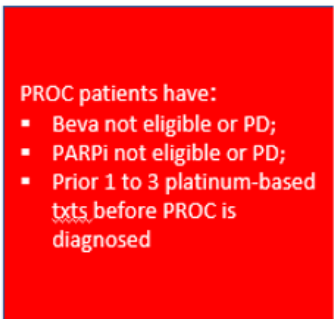
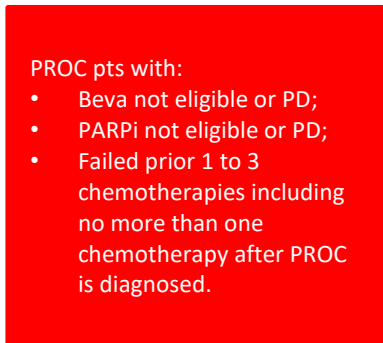
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Note. Reprinted from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guidelines (version 1.1). Eur J Cancer. 2009; 45(2):228-247.

Protocol LAE002INT2001/Changes for Protocol Version 3.0 to Version 4.0

Page/Section	Version 3.0	Version 4.0
Page 1 TITLE PAGE	Effective Date: 28 February 2020 Copyright 2019 Laekna Limited. All rights reserved. Unauthorized copying or use of this information is prohibited.	Effective Date: 28 February ~~2020~~ November 2020 Copyright ~~2019~~ 2020 Laekna Limited. All rights reserved. Unauthorized copying or use of this information is prohibited.
Page 2 SPONSOR SIGNATORY	I, the undersigned, have reviewed and approved version 3.0 of the clinical study protocol with the date of 28 February 2020.	I, the undersigned, have reviewed and approved version ~~3.0~~ 4.0 of the clinical study protocol with the date of ~~1228 February~~ November 2020 .
Page 4 LIST OF STUDY PERSONNEL	Medical Monitor: Ying Bian, MD Executive Medical Director Laekna Limited Unit 417, 4 th Floor, Lippo Centre, Tower Two, No. 89 Queensway, Admiralty, Hong Kong Email: ying.bian@laeknatp.com Phone: +1- 203-329-8287	Medical Monitor: ~~Ying Bian, MD~~ ~~Executive Medical Director~~ ~~Laekna Limited~~ ~~Unit 417, 4th Floor, Lippo Centre,~~ ~~Tower Two, No. 89 Queensway, Admiralty,~~ ~~Hong Kong~~ ~~Email: ying.bian@laeknatp.com~~ ~~Phone: +1- 203-329-8287~~ Xiaoyu Wang, MD, PhD Associate Medical Director Laekna Limited Unit 417, 4th Floor, Lippo Centre, Tower Two, No. 89 Queensway, Admiralty, Hong Kong Email: xiaoyu.wang@laeknatp.com

		Phone: +1- 201-300-7139 Vivian Liu, MD, PhD Medical Director Laekna Limited Unit 417, 4th Floor, Lippo Centre, Tower Two, No. 89 Queensway, Admiralty, Hong Kong Email: vivian.liu@laeknatp.com Phone: +86-15216741842
Page 15&17/1.1 Synopsis	However, the study population in the above studies were different from the patient population in this Phase II study because the current Phase II study targets the PROC patients who took 1 to 3 prior platinum-based therapies.	However, the study population in the above studies were different from the patient population in this Phase II study because the current Phase II study targets the PROC patients who took 1 to 3 prior ~~platinum-based therapies~~ chemotherapies including no more than one chemotherapy after PROC was diagnosed.
Page 15/1.1 Synopsis	Currently, there are limited treatment options in clinical management for PROC patients who have had 1 to 3 prior platinum-based therapies and who have failed bevacizumab and/or PARP inhibitor.	Currently, there are limited treatment options in clinical management for PROC patients who have had 1 to 3 ~~prior platinum-based therapies~~ chemotherapies including no more than one chemotherapy after PROC was diagnosed and who have failed bevacizumab and/or PARP inhibitor.
Page 18/1.1 Synopsis Page 32/4.1 Overall Design	Patients must have been treated with 1 to 3 prior platinum-based chemotherapy regimens (combination therapy will be considered as one treatment, whereas maintenance therapy will be considered as the continuation of previous systemic treatment; no other	Patients must have been treated with 1 to 3 prior ~~platinum-based chemotherapy regimens~~ chemotherapies 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

	treatment is allowed except for PARP inhibitor or bevacizumab) before the PROC was diagnosed and must have progressed or relapsed between 1 to 6 months after the last dose of platinum-based therapy (at least 4 cycles).	the continuation of previous systemic treatment; ~~no other treatment is allowed except for~~ , such as PARP inhibitor or bevacizumab are considered as maintenance therapy). ~~before the PROC was diagnosed and~~ Patient's OC must have progressed or relapsed between 1 to 6 months after the last dose of platinum-based therapy (at least 4 cycles).
Page 19/1.1 Synopsis Page 86/10.2 Sample Size Determination	The primary endpoint of this study is PFS. Previous studies ^{2,3,4} have shown that PROC patients have a median PFS of around 3.5 months with weekly paclitaxel after 1 to 3 prior platinum-based chemotherapies before PROC was diagnosed.	The primary endpoint of this study is PFS. Previous studies ^{2,3,4} have shown that PROC patients have a median PFS of around 3.5 months with weekly paclitaxel after 1 to 3 prior ~~platinum-based chemotherapies before~~ chemotherapies including no more than one chemotherapy after PROC was diagnosed.
Page 19/1.2 Schema	 PROC patients have: ▪ Beva not eligible or PD; ▪ PARPi not eligible or PD; ▪ Prior 1 to 3 platinum-based txs before PROC is diagnosed	 PROC pts with: • Beva not eligible or PD; • PARPi not eligible or PD; • Failed prior 1 to 3 chemotherapies including no more than one chemotherapy after PROC is diagnosed.
Page 26/2.3 Study Rationale	There are no clinical data for the combinations of afuresertib plus weekly paclitaxel in patients with PROC, especially in those who failed 1 to 3 prior platinum-based	There are no clinical data for the combinations of afuresertib plus weekly paclitaxel in patients with PROC, especially in those who failed 1 to 3 prior ~~platinum-based therapies~~

	therapies, bevacizumab and/or PARP inhibitor. It is critical to understand the safety and anticancer efficacy of the afuresertib plus weekly paclitaxel combination.	chemotherapies (no more than one chemotherapy after PROC was diagnosed) with; bevacizumab and/or PARP inhibitor. It is critical to understand the safety and anticancer efficacy of the afuresertib plus weekly paclitaxel combination.
Page 27/ 2.5.2 Other Toxicities Based on Clinical Experience	Careful glucose monitoring will be implemented, particularly during the first cycle of therapy.	~~Careful glucose monitoring will be implemented, particularly during the first cycle of therapy~~ through the whole therapy process, according to the clinical judgement by the investigator.
Page 33/ Inclusion Criteria	6. The OC patients must have received 1 to 3 prior platinum-based regimens before PROC was diagnosed. No other additional anticancer treatment is allowed except for PARP inhibitor or bevacizumab. Combination therapy will be considered as one treatment, whereas maintenance therapy will be considered as continuation of the previous systemic treatment. Patients should be appropriate candidates for treatment with single agent weekly paclitaxel based on investigator's clinical assessment.	6. The OC patients must have received 1 to 3 prior ~~platinum-based regimens before~~ chemotherapies including no more than one chemotherapy after PROC was diagnosed. No other additional anticancer treatment is allowed except for PARP inhibitor or bevacizumab. Combination therapy with two or more drugs will be considered as one treatment, whereas maintenance therapy will be considered as continuation of the previous ~~systemic treatment~~ therapy . Patients should be appropriate candidates for treatment with single agent weekly paclitaxel based on investigator's clinical assessment.
Page 33/ Inclusion Criteria	7. Patients must either have received prior treatments with bevacizumab followed by disease progression, or bevacizumab cannot be used because of a specific condition, as listed (patients not treated with prior bevacizumab because of a condition may represent no more than 10% of the total number enrolled): History of GI bleeding, ulceration, or fistula	7. Patients must either have received prior treatments with bevacizumab followed by disease progression, or bevacizumab cannot be used, or discontinued to use because of a specific condition, as listed (patients not ~~treated with prior~~ eligible for or discontinued bevacizumab because of a condition may represent no more than ~~10%~~ 20% of the total number enrolled): History of GI bleeding, ulceration, or fistula

	• Reversible Posterior Leukoencephalopathy Syndrome (RPLS) • Proteinuria • Infusion reaction	• Reversible Posterior Leukoencephalopathy Syndrome (RPLS) • Proteinuria • Infusion reaction • Any radiographic evidence of bowel (gastrointestinal tract) involvement • Hemorrhage: Grade 3-4 hemorrhage • Hypertension: hypertensive crisis or hypertensive encephalopathy • Arterial Thromboembolic Events: severe arterial thromboembolic events • Venous Thromboembolic Events: Grade 4 thromboembolic events
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Page 43/Table 3. Dose Modification Guidance	Afuresertib (LAE002)CONFIDENTIALProtocol: LAE002INT2001 <table><tr><th rowspan="2">Toxicity</th><th rowspan="2">Grade or Value</th><th colspan="2">Dose Modification Suggestions</th></tr><tr><th>Afuresertib</th><th>Paclitaxel</th></tr><tr><td>Other grade ≥ 3 non-hematological toxicity except rash (Section 6.8.3). See also details on grade 3-4 mucositis in Section 6.9.2.</td><td>Grade ≥ 3</td><td>Hold treatment. If resolved to baseline in < 14 days, consider dose reduction by 25 mg. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.</td><td>Hold treatment. If resolved to baseline in <14 days, consider dose reduction of 20%. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.</td></tr></table> ANC = Absolute neutrophil count	Toxicity	Grade or Value	Dose Modification Suggestions		Afuresertib	Paclitaxel	Other grade ≥ 3 non-hematological toxicity except rash (Section 6.8.3). See also details on grade 3-4 mucositis in Section 6.9.2.	Grade ≥ 3	Hold treatment. If resolved to baseline in < 14 days, consider dose reduction by 25 mg. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.	Hold treatment. If resolved to baseline in <14 days, consider dose reduction of 20%. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.	Afuresertib (LAE002)CONFIDENTIALProtocol: LAE002INT2001 <table><tr><th rowspan="2">Toxicity</th><th rowspan="2">Grade or Value</th><th colspan="2">Dose Modification Suggestions</th></tr><tr><th>Afuresertib</th><th>Paclitaxel</th></tr><tr><td rowspan="3">Diarrhea or Fatigue or Skin rash</td><td>Grade 1</td><td>Consider dose regimen change from 125 mg QD to 125 mg D1-5, Q1W.</td><td>None</td></tr><tr><td>Grade ≥ 2</td><td>Hold treatment until resolved to grade 1.</td><td>None</td></tr><tr><td>Grade ≥ 3</td><td>Hold treatment until resolved to grade 1.</td><td>Hold treatment until resolved to grade 2.</td></tr><tr><td>Other grade ≥ 3 non-hematological toxicity except rash (Section 6.8.3). See also details on grade 3-4 mucositis in Section 6.9.2.</td><td>Grade ≥ 3</td><td>Hold treatment. If resolved to baseline in < 14 days, consider dose reduction by 25 mg. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.</td><td>Hold treatment. If resolved to baseline in <14 days, consider dose reduction of 20%. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.</td></tr></table> ANC = Absolute neutrophil count	Toxicity	Grade or Value	Dose Modification Suggestions		Afuresertib	Paclitaxel	Diarrhea or Fatigue or Skin rash	Grade 1	Consider dose regimen change from 125 mg QD to 125 mg D1-5, Q1W.	None	Grade ≥ 2	Hold treatment until resolved to grade 1.	None	Grade ≥ 3	Hold treatment until resolved to grade 1.	Hold treatment until resolved to grade 2.	Other grade ≥ 3 non-hematological toxicity except rash (Section 6.8.3). See also details on grade 3-4 mucositis in Section 6.9.2.	Grade ≥ 3	Hold treatment. If resolved to baseline in < 14 days, consider dose reduction by 25 mg. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.	Hold treatment. If resolved to baseline in <14 days, consider dose reduction of 20%. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.
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Page 61/ Table 8. Time and Events Table	Fingerstick blood glucose: <table><tr><td>At home daily during first 3 weeks of therapy^(c)</td><td>As clinically needed^(c)</td></tr></table>	At home daily during first 3 weeks of therapy ^(c)	As clinically needed ^(c)	Fingerstick blood glucose: <table><tr><td>At home during therapy (the frequency of the test will be decided by the investigator based on clinical judgement)^(c)</td></tr></table>	At home during therapy (the frequency of the test will be decided by the investigator based on clinical judgement) ^(c)																											
At home daily during first 3 weeks of therapy ^(c)	As clinically needed ^(c)																															
At home during therapy (the frequency of the test will be decided by the investigator based on clinical judgement) ^(c)																																
Page 63/ Table 8. Time and Events Table Notes:	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.	21. Patient must record in a diary each day: study drug dosing, AEs, concomitant medication dosing, and glucose level (fingerstick) if recommended by study physician . Patients should bring the diary to each visit for site review.																														

Summary of Changes

From Version 4.0 to Version 5.0

Page/ Section/ Lines in new version	Version 4.0	Version 5.0
Title page/ Document version number		Added: "Document Version Number: 5.0"
Title page/ Effective date	28 November 2020	20 September 2021
Title page/ Authors	Haige Shen	Juan Liu
Title page	Copyright 2020 Laekna Limited.	Copyright 2021 Laekna Limited.
Title page/ Sponsor Signature	I, the undersigned, have reviewed and approved version 4.0 of the clinical study protocol with the date of 12 November 2020.	I, the undersigned, have reviewed and approved version 5.0 of the clinical study protocol with the date of 20 September 2021 .
Title page/ Sponsor Signatory/ Date	Nov. 12, 2020	20 September, 2021
Page 13 Ln 1	~~PPS~~ ~~Per Protocol Set~~	Deleted
Page 15/ Rationale/ Ln 1	...treated with chemotherapy alone	...treated with paclitaxel alone
Page 15/ Rationale/ Ln 3	These results of PFS may be appropriate candidates for the historical control PFS in the present Phase II study exploring afuresertib combination therapy.	Therefore, the median PFS with paclitaxel in multiple lines setting from 6 clinical trials averaged 3.5 months⁴³. These PFS results may be an appropriate benchmark for the control arm in the present Phase II study exploring the addition of afuresertib to weekly paclitaxel.
Page 15/ Rationale/ Ln 7	...the current Phase II study targets the PROC patients who took 1 to 3 prior chemotherapies...	...the current Phase II study targets the PROC patients who have had 1 to 5 prior chemotherapies
Page 15/ Rationale/ Ln 9	In addition, in the current study, patients may have or have not taken bevacizumab and/or a PARP inhibitor, if appropriate, but their OC progressed.	In addition, patients in the current study may or may not have been treated with bevacizumab previously.
Page 15/ Rationale/ Ln 10	The PFS of PROC patients treated with weekly paclitaxel alone in the above historical controls had either only 1 prior platinum-based therapy or 1 or 2 prior treatments.	The PROC patients treated with weekly paclitaxel alone in the above historical controls had either at least 1 prior platinum-based therapy or 1 to 4 prior non-platinum-based treatments.
Page 15/ Rationale/ Ln 13	...but logically closer to the lower end...	...but would logically be closer to the lower end...
Page 15/ Rationale/ Ln 17	Currently, there are limited treatment options in clinical management for PROC patients who have had 1 to 3 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed and who may have failed bevacizumab and/or PARP inhibitor or never take bevacizumab and/or PARP inhibitor.	Currently, there are limited treatment options in clinical management for PROC patients who have had 1 to 5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed and who may or may not have been treated with bevacizumab previously.

Page/ Section/ Lines in new version	Version 4.0	Version 5.0
Page 17/ Study Hypothesis/ Ln 8	... who took 1 to 3 prior chemotherapies...	... who have had 1 to 5 prior chemotherapies...
Page 17/ Study Hypothesis/ Ln 9	In addition, in the current study, patients may have taken bevacizumab and/or a PARP inhibitor, if appropriate, but their OC progressed anyway.	In addition, patients may or may not have been treated with bevacizumab previously.
Page 17/ Study Hypothesis/ Ln 10	The PFS of PROC patients treated with weekly paclitaxel alone in the above historical control had either only 1 prior platinum-based therapy or 1 or 2 prior treatments.	The PROC patients treated with weekly paclitaxel alone in the above historical control had either at least 1 prior platinum-based therapy or 1 to 4 prior non-platinum-based treatments.
Page 17/ Study Hypothesis/ Ln 13	...but logically closer to the lower end of the PFS range	...but would logically be closer to the lower end of the PFS range
Page 17/ Study Hypothesis/ Ln 19	The study combination therapy of afuresertib plus weekly paclitaxel has no close reference	The study combination therapy of afuresertib plus weekly paclitaxel lacks historical reference
Page 17/ Study Hypothesis/ Ln 25	... although the Phase I/II study enrolled more patients with > 3 prior lines of treatments, whereas the current Phase II study will enroll the PROC patients are either not eligible to take bevacizumab and/or PARP inhibitor or those whose cancer progress despite treatment with bevacizumab and/or PARP inhibitor.	... in that the Phase I/II study enrolled patients with 1-7 prior lines of treatments, and the current Phase II study will enroll PROC patients who have had 1-5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed.
Page 18/ Study Hypothesis/ Ln 2	Therefore, it is expected that the planned Phase II Study LAE002INT2001 will have a PFS of 6.5 months in the PROC population ...	Therefore, it is expected that the planned Phase II Study LAE002INT2001 will have a PFS of approximately 6.5 months in the PROC population ...
Page 18/ Study Hypothesis/ Ln 9	$H_0: PFS_{comb} \leq PFS_{ctrl}$ versus $H_a: PFS_{comb} > PFS_{ctrl}$	$H_0: PFS_{comb} = PFS_{ctrl}$ versus $H_a: PFS_{comb} \neq PFS_{ctrl}$
Page 18/ Study Design/ Ln 13	The randomization will be stratified by site, country : [US] vs. China, duration of the platinum free interval (PFI): 1-3 months vs >3-6 months, and number of prior platinum based therapy treatments (1-2 versus 3 prior platinum regimens).	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 vs. 3-5 prior platinum regimens).
Page 18/ Study Design/ Ln 23	Patients will be tested at baseline for phosphoinositide 3 kinase (PI3K)/AKT/PTEN pathway alterations, BRCA1/2 mutations, and/or level of phosphor-AKT by IHC	Patients will be tested at baseline for phosphoinositide 3 kinase (PI3K)/AKT/PTEN pathway alterations and BRCA1/2 mutations by NGS, and/or level of phosphor-AKT by IHC
Page 18/ Study Design/ Ln 33	Patients must have been treated with 1 to 3 prior 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	Patients must have had 1 to 5 prior chemotherapies 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

Page/ Section/ Lines in new version	Version 4.0	Version 5.0
	previous systemic treatment, such as PARP inhibitor or bevacizumab are considered as maintenance therapy following chemotherapy).	treatment, such as PARP inhibitor or bevacizumab are considered as maintenance therapy following chemotherapy.
Page 18/ Study Design/ Ln 37	Patient's OC must have progressed or relapsed between 1 to 6 months after the last dose of platinum-based therapy (at least 4 cycles).	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.
Page 19/ Sample size estimation and statistical analysis methodology/ Ln 17	... after 1 to 3 prior chemotherapies	... after 1 to 5 prior chemotherapies
Page 19/ Sample size estimation and statistical analysis methodology/ Ln 19	The combination therapy is expected to result in an improved median PFS of 6.5 months, i.e. a 46% reduction of the disease progression risk.	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.
Page 19/ Sample size estimation and statistical analysis methodology/ Ln 20	In the primary analysis, PFS of patients will be compared between the patients treated with the combination therapy and the monotherapy of paclitaxel using the unstratified log-rank test.	Text deleted.
Page 19/ Sample size estimation and statistical analysis methodology/ Ln 21	With the one-sided type I error rate controlled at 0.025, a total of 105 events are needed to provide about 85% statistical power to test the difference between the 2 therapies.	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.
Page 19/ Sample size estimation and statistical analysis methodology/ Ln 29	The primary statistical analysis will be based on a stratified log-rank test using the stratification variables (with exception of site) at randomization in the model. The hazard ratio and 95% CI will be calculated based on a stratified Cox proportional hazards model using the same stratification variables (with exception of site) at randomization.	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.
Page 20/ Section 1.2 Schema	PROC pts with: • Beva not eligible or PD; • PARPi not eligible or PD; • Failed prior 1 to 3 chemotherapies including no more than one chemotherapy after PROC was diagnosed.	PROC pts who : • Failed 1 to 5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed. • May or may not have had prior Beva treatment

Page/ Section/ Lines in new version	Version 4.0	Version 5.0
Page 25/ Section 2.3 Study Rationale/ Ln 31	There are no clinical data for the combinations of afuresertib plus weekly paclitaxel in patients with PROC, especially in those who failed 1 to 3 prior chemotherapies (no more than one chemotherapy after PROC was diagnosed) with bevacizumab and/or PARP inhibitor.	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 chemotherapies (no more than one chemotherapy after PROC was diagnosed) with or without prior bevacizumab treatment.
Page 28/ Nervous System/ Ln 1	Patients with pre-existing neuropathy at or above grade 2 at screening will not be allowed to participate.	Patients with pre-existing neuropathy greater than grade 2 at screening will not be allowed to participate.
Page 31/ Section 4.1 Overall Design/ Ln 7	The randomization will be stratified by site, country : [US] vs. China, duration of the platinum free interval (PFI): 1-3 months vs >3-6 months, and number of prior platinum based therapy treatments (1-2 versus 3 prior platinum regimens).	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 vs. 3-5 prior platinum regimens).
Page 31/ Section 4.1 Overall Design/ Ln 16	The third period is a Follow-up Period (safety evaluation at 30 days after the last dose of study treatment and OS and PFS follow up).	The third period is a Follow-up Period (safety evaluation at 30 days after the last dose of study treatment and OS and/or PFS follow up).
Page 31/ Section 4.1 Overall Design/ Ln 17	Patients will be tested at baseline for PI3K/AKT/PTEN pathway alterations, BRCA1/2 mutation, and/or level of phospho-AKT by IHC	Patients will be tested at baseline for PI3K/AKT/PTEN pathway alterations and BRCA1/2 mutations by NGS, and/or level of phospho-AKT by IHC
Page 31/ Section 4.1 Overall Design/ Ln 27	Patients must have been treated with 1 to 3 prior chemotherapy regimens (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 maintenance therapy).	Patients must have had 1 to 5 prior 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 maintenance therapy.
Page 31/ Section 4.1 Overall Design/ Ln 31	In addition, patient's OC must have progressed or relapsed between 1 to 6 months after the last dose of platinum-based therapy (at least 4 cycles).	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.
Page 33/ Section 5.1.2 Inclusion Criteria/ Ln 26	5. Must have PROC (including fallopian tube and primary peritoneal carcinoma), defined as cancer progression between 1 month and 6 months after completion of the prior platinum-based therapy (at least 4 cycles), < 6 months for those failed. ~~Progression is defined by RECIST 1.1 criteria in association with symptoms necessitating treatment (Appendix 3).~~	5. Must have PROC (including fallopian tube and primary peritoneal carcinoma), defined as disease relapsed between 1 to 6 months after the last dose of the first-line prior platinum-based therapy (at least 3 cycles), or progressed during or relapsed within 6 months of the last dose of platinum-based < 6 months for those failed 2nd-5th line therapies.
Page 33/ Section 5.1.2 Inclusion Criteria/ Ln 29	6. The OC patients must have received 1 to 3 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed.	6. The OC patients must have received 1 to 5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed.

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	~~No other additional anticancer treatment is allowed except for PARP inhibitor or bevacizumab. Combination therapy with two or more drugs will be considered as one therapy, whereas maintenance therapy will be considered as continuation of the previous systemic treatment. Patients should be appropriate candidates for treatment with single agent weekly paclitaxel based on investigator's clinical assessment.~~	
Page 33/ Section 5.1.2 Inclusion Criteria/ Ln 30	No other additional anticancer treatment is allowed except for PARP inhibitor or bevacizumab.	Text deleted
Page 33/ Section 5.1.2 Inclusion Criteria/ Ln 34	~~7. Patients must either have received prior treatments with bevacizumab followed by disease progression, or bevacizumab cannot be used, or discontinued to use because of a specific condition, as listed (patients not eligible for or discontinued bevacizumab because of a condition may represent no more than 20% of the total number enrolled patients):~~ ~~• History of GI bleeding, ulceration, or fistula~~ ~~• Reversible Posterior Leukoencephalopathy Syndrome (RPLS)~~ ~~• Proteinuria~~ ~~• Infusion reaction~~ ~~• Any radiographic evidence of bowel (gastrointestinal tract) tumor involvement~~ ~~• Hemorrhage: Grade 3-4 hemorrhage~~ ~~• Hypertension: hypertensive crisis or hypertensive encephalopathy~~ ~~• Arterial Thromboembolic Events: severe arterial thromboembolic events~~ ~~• Venous Thromboembolic Events: Grade 4 thromboembolic events~~	Old criterion #7 deleted. Replaced with new criterion #7 (separated from previous criterion #6) “Patients should be appropriate candidates for treatment with single agent weekly paclitaxel based on investigator's clinical assessment.”
Page 33/ Section 5.1.2 Inclusion Criteria/ Ln 35	8. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1	8. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
Page 34/ Section 5.1.2 Inclusion Criteria/ Ln 12	14. Patients must be able to tolerate oral medications and not have any GI illnesses that would preclude absorption of afuresertib.	14. Patients must have GI functions that would allow absorption of afuresertib.
Page 34/ Section 5.1.3 Exclusion Criteria/ Ln 28	1. Platinum refractory disease (progression during or less than 1 month of receiving previous platinum-containing therapy).	1. Primary platinum-refractory disease, defined as “disease progression during or relapsed within 1 month after the last dose of the first -line platinum-based therapy”.

Page/ Section/ Lines in new version	Version 4.0				Version 5.0			
Page 35/ Section 5.1.3 Exclusion Criteria/ Ln 13	14. History or evidence for any of the following: severe or unstable angina ~~or~~ myocardial infarction.				14. History or evidence for any of the following: severe or unstable angina, myocardial infarction.			
Page 39/ Section 6.3 Treatment Assignment/ Ln 2	Randomization will be stratified by site, country (United States [US], China). In addition, the randomization will also be stratified by the duration of the PFI: 1-3 months vs >3-6 months use of and number of prior platinum-based therapy treatments (1-2 versus 3 prior platinum regimens).				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 vs. 3-5 prior platinum regimens).			
Page 39/ Ln 3	Each site will be given a patient number range.				Text deleted.			
Page 40/ Section 6.7 Patient Discontinuation/ Ln 6	• A clinically significant AE caused by a study drug leading to an interruption of treatment for greater than 14 days. For patients for whom the treatment has been interrupted, the investigator should consult the Study Medical Monitor to discuss the possibility of discontinuing treatment after 14 days of treatment hold. If the investigator and a Study Medical Monitor conclude that continued treatment could benefit a patient who has a greater than a 14-day treatment delay, then the patient will be allowed to continue therapy with the approval of the Study Medical Monitor.				• A clinically significant AE caused by the study drug(s) leading to an interruption of both study drugs for greater than 14 consecutive days. In such case, the investigator should consult the Study Medical Monitor to discuss the possibility of discontinuing treatment. If the investigator and a Study Medical Monitor conclude that continued treatment could benefit a patient who has a greater than a 14 consecutive days of treatment delay, then the patient will be allowed to continue therapy with the approval of the Study Medical Monitor.			
Page 41/ Section 6.8 Dose Adjustment/Stopping Criteria/ Ln 13	A maximum of two dose reductions per study drug are allowed during the study.				A maximum of two dose level modifications per study drug are allowed during the study.			
Page 41/ Section 6.8 Dose Adjustment/Stopping Criteria/ Ln 13	Requirement for a third dose reduction of a particular study drug would necessitate discontinuing the study drug.				Text deleted.			
Page 41/ Table 3. Dose Modification Guidance	Toxicity	Grade or Value	Dose Modification Suggestions		Toxicity	Grade or Value	Dose Modification Suggestions	
			Afuresertib	Paclitaxel			Afuresertib	Paclitaxel
	Platelets	≥ 50,000/ µl to < 100,000/µl	None	Hold treatment until platelet count is ≥ 100,000/µl. Recommend repeat platelet count in 1 week	Platelets	≥ 50,000/ µl to < 100,000/µl	None	Hold treatment until platelet count is ≥ 100,000/µl. Recommend repeat platelet count in 1 week

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				if treatment held. Consider reduction in dose by at least 20%.				if treatment held. Consider reduction in dose by at least 20%.
		< 50,000/ μ l	Hold treatment until platelet count is $\geq 100,000/\mu$ l. Recommend repeat platelet count in 1 week if treatment held. Consider dose reduction to 100 mg if after dose reduction in chemotherapy component, nadir platelet count again decreases to <50,000/ μ L.	Hold treatment until platelet count is $\geq 100,000/\mu$ l. Recommend repeat platelet count in 1 week if treatment held. Consider reduction in dose by at least 20%.		< 50,000/ μ l	Hold treatment until platelet count is $\geq 100,000/\mu$ l. Recommend repeat platelet count in 1 week if treatment held. Consider dose reduction to 125 mg D1-4, Q7D , if after dose reduction in chemotherapy component, nadir platelet count again decreases to <50,000/ μ L.	Hold treatment until platelet count is $\geq 100,000/\mu$ l. Recommend repeat platelet count in 1 week if treatment held. Consider reduction in dose by at least 20%.
	ANC	$\geq 500/\text{mm}^3$ to < 1500/ mm^3	None	Hold treatment until ANC is $\geq 1500/\text{mm}^3$. Recommend repeat ANC in 1 week if treatment held.	ANC	$\geq 500/\text{mm}^3$ to < 1500/ mm^3	None	Hold treatment until ANC is $\geq 1500/\text{mm}^3$. Recommend repeat ANC in 1 week if treatment held.

Page/ Section/ Lines in new version	Version 4.0				Version 5.0			
		< 500/mm ³	Hold treatment until ANC is $\geq 1500/\text{mm}^3$. Recommend repeat ANC in 1 week if treatment held. Consider reduction of dose by 25 mg.	Hold treatment until ANC is $\geq 1500/\text{mm}^3$. Recommend repeat ANC in 1 week if treatment held. Consider reduction of dose by at least 20%.		< 500/mm ³	Hold treatment until ANC is $\geq 1500/\text{mm}^3$. Recommend repeat ANC in 1 week if treatment held. Consider 125 mg D1-4 Q7D if ANC $\geq 1500/\text{mm}^3$; then return to 125 mg QD if ANC $\geq 1500/\text{mm}^3$ for 1 week.	Hold treatment until ANC is $\geq 1500/\text{mm}^3$. Recommend repeat ANC in 1 week if treatment held. Consider reduction of dose by at least 20%.
	Febrile neutropenia (38.5°C for 48 hours or longer)		If resolved < 5 days, consider reducing dose by 25 mg.	If resolved < 5 days, reduce dose by 20% (following ANC recommendations).	Febrile neutropenia (ANC <1000/mm ³ and a single temperature of >38.3°C or a sustained temperature of $\geq 38^\circ\text{C}$ for more than one hour.)		Hold treatment. If fever resolves in 5 days, consider 125 mg D1-4 Q7D if ANC $\geq 1500/\text{mm}^3$; then return to 125 mg QD (following ANC recommendations).	Hold treatment If fever resolves in 5 days, consider reduction of dose by 20% (following ANC recommendations).
		Grade 1	None	None		Grade 1	None	None

Page/ Section/ Lines in new version	Version 4.0				Version 5.0			
		Grade 2	None	Hold treatment until toxicity resolves to baseline. Consider at least 20% dose reduction.	Peripheral sensory neuropathy	Grade 2	None	Hold treatment until toxicity resolves to baseline. Consider at least 20% dose reduction.
		Grade 3	None	Hold treatment until toxicity resolves to grade 1 or less. Consider discontinuation of paclitaxel.		Grade 3	None	Hold treatment until toxicity resolves to grade 1 or less. Consider discontinuation of paclitaxel.
		Grade 4	Withdraw patient from study.	Withdraw patient from study.		Grade 4	Withdraw patient from study.	Withdraw patient from study.
	Hyperglycemia (see also Section 6.8.4)	Grade 1-2	None	None	Hyperglycemia (see also Section 6.8.4)	Grade 1-2	None	None
		Grade 3	Hold treatment. If resolved to grade 1 < 14 days, reduce dose by 25 mg.	None		Grade 3	Hold treatment. If resolved to grade 1 in 14 days, consider 125 mg, D1-4 Q7D for 1 week, then return to 125 mg QD.	None
		Grade 4 or ketoacidosis	Withdraw patient from study.	Withdraw patient from study.		Grade 4 or ketoacidosis	Withdraw patient from study.	Withdraw patient from study.

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	Anaphylaxis (acute hypersensitivity reactions)	Severe reactions defined as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria.	None unless afuresertib is the only study drug being taken by the patient. In that case, immediately discontinue treatment and do NOT rechallenge.	Immediately discontinue treatment and do NOT rechallenge.	Anaphylaxis (acute hypersensitivity reactions)	Severe reactions defined as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria.	None unless afuresertib is the only study drug being taken by the patient. In that case, immediately discontinue treatment and do NOT rechallenge.	Immediately discontinue treatment and do NOT rechallenge.
	Conduction disorder	Grade 1 and 2	None	None	Conduction disorder	Grade 1 and 2	None	None
		Grade ≥ 3	None	Immediately discontinue treatment and do NOT rechallenge. Provide supportive care as needed.		Grade ≥ 3	None	Immediately discontinue treatment and do NOT rechallenge. Provide supportive care as needed.
	Diarrhea or Fatigue or Skin rash	Grade 1	Consider dose regimen change from 125 mg	None	Diarrhea or Fatigue or Skin rash	Grade 1	Consider dose reduction to 125 mg D1-4, Q7D. Consider to return to 125 mg QD if	None

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			QD to 125 mg QD D1-5 Q1W.				resolved to baseline.	
		Grade ≥ 2	Hold treatment until resolved to grade 1.	None		Grade ≥ 2	Hold treatment until resolved to grade 1.	None
		Grade ≥ 3	Hold treatment until resolved to grade 1.	Hold treatment until resolved to grade 2.		Grade ≥ 3	Hold treatment until resolved to grade 1.	Hold treatment until resolved to grade 2.
	Other grade ≥ 3 non-hematologic al toxicity except rash (Section 6.8 .3). See also details on grade 3-4 mucositis in Section 6.9. 2.	Grade ≥ 3	Hold treatment. If resolved to baseline in < 14 days, consider dose reduction by 25 mg. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.	Hold treatment. If resolved to baseline in <14 days, consider dose reduction of 20%. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.	Other grade ≥ 3 non-hematologic al toxicity except rash (Section 6.8 .3). See also details on grade 3-4 mucositis in Section 6.9. 2.	Grade ≥ 3	Hold treatment. If resolved to baseline in 14 days, consider 125 mg D1-4, Q7D for 1 week. Consider to return to 125 mg QD in next cycle if no recurrence or new toxicities.	Hold treatment. If resolved to baseline in <14 days, consider dose reduction of 20%. Consider re-escalation to full dose in next cycle if no recurrence or new toxicities.
Page 44/ Section 6.8.1 Liver Chemistry Stopping Criteria/ Ln 13	• Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE				• Complete the SAE data collection tool if the event also meets the criteria for an SAE			
Page 44/ Section 6.8.1 Liver Chemistry Stopping Criteria/ Ln 18	• Complete the liver imaging and/or liver biopsy CRFs if these tests are performed				Text deleted			

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Page 44/ Section 6.8.1 Liver Chemistry Stopping Criteria/ Ln 19	• Perform liver event follow-up assessments, and monitor the patient until liver chemistries resolve, stabilize, or return to baseline values, as described below	• Perform follow-up assessments, and monitor the patient until liver chemistries resolve, stabilize, or return to baseline values, as described below
Page 47/ Grade 1 rash/ Ln 17	Continue current dose of study drug.	Consider afuresertib dose reduction from 125 mg QD to 125 mg D1-4, Q7D.
Page 47/ Grade 1 rash/ Ln 21		Added text: Consider to return afuresertib dose to 125 mg QD if rash resolves to baseline.
Page 47/ Grade 2 rash/ Ln 23	Continue current dose of study drug.	Consider temporary discontinuation of afuresertib until rash resolves to grade 1.
Page 47/ Grade 2 rash/ Ln 29	Once rash resolves, consider re-escalation to previously tolerated dose.	Text deleted
Page 48/ Grade 3-4 rash/ Ln 4	Consider temporary discontinuation of study drug dosing if systemic steroids do not provide symptomatic relief.	Consider temporary discontinuation of both study drugs until rash resolves to grade 1 (for afuresertib) or grade 2 (for paclitaxel) , if systemic steroids do not provide symptomatic relief.
Page 48/ Grade 3-4 rash/ Ln 6	Once rash resolves, if study drug was held, consider reducing study drug dose by 25 mg. Consider re-escalation to previously tolerated dose at next study cycle if symptoms resolve to baseline with dose reduction.	Text deleted
Page 49/ Recommended management of uncomplicated grade 1-2 diarrhea/ Ln 1		Added text: • For grade 1 diarrhea, consider afuresertib dose reduction from 125 mg QD to 125 mg D1-4, Q7D. Consider to return to 125 mg QD if diarrhea resolves to baseline.
Page 49/ Recommended management of uncomplicated grade 1-2 diarrhea/ Ln 3	• Temporarily discontinue use of study drug for grade 2 diarrhea and consider a dose reduction (discuss with Laekna Limited or CRO Medical Monitor).	• For grade 2 diarrhea, temporarily discontinue afuresertib until diarrhea resolves to grade 1.
Page 49/ Recommended management of grade 3-4 diarrhea/ Ln 11	• Temporarily discontinue use of study drug and discuss with Laekna Limited or CRO Medical Monitor	• Temporarily discontinue both study drugs until diarrhea resolves to grade 1 (for afuresertib) or grade 2 (for paclitaxel) and discuss with Laekna Limited or CRO Medical Monitor
Page 52/ Section 7.2 Prohibited Medications and Non-Drug Therapies/ Ln 1	Erythropoiesis-stimulating agents and colony-stimulating factors like filgrastim and pegfilgrastim are prohibited during the first 3 weeks of combination dosing, although they may be used as clinically indicated in subsequent weeks. Pegfilgrastim should not be used in combination with weekly paclitaxel.	Text deleted

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Page 56/ Section 8 STUDY ASSESSMENTS AND PROCEDURES/ Ln 13	Select assessments throughout the study are calendar-based,	Certain assessments throughout the study are calendar-based,
Page 57/ Table 8	Header for Cycle 1 Day 1: “Cycle 1 Day 1 (~~4 days~~)”	Deleted “(4 days)” in the header for Cycle 1 Day 1: “Cycle 1 Day 1” Footnote “7” added to “Physical exam”, ECOG performance status” on Cycle 1 Day1 assessments. Footnote “24” added to “Randomization” on Cycle 1 Day1 assessment.
Page 60/ Notes	2. All screening assessments must be completed within 14 days prior to the first dose, except tumor assessments, which can occur within 28 days prior to the first dose.	2. 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.
Page 61/ Notes	23. The investigator may report any AE that he/she believes is possibly related to study treatment.	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.
Page 61/ Notes		Added text: Added footnote: 24. Randomization could be performed up to 4 days prior to C1D1 (Day -4 to Day 1 of Cycle 1).
Page 64/ Section 8.2.1.2 Definition of a SAE/ Ln 2	e. Results in a congenital anomaly/birth defect in the offspring of a patient who received study drug. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.	e. Results in a congenital anomaly/birth defect in the offspring of a patient who received study drug. f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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	f. Protocol-specific SAEs:	g. Protocol-specific SAEs:
Page 65/ 8.2.1.6 Assessment of Causality/ Ln 23		Added text: The causality between adverse events and the investigational drug may be evaluated as: - “Related”, i.e., there is reasonable possibility, or - “Unrelated”, i.e., there is no reasonable possibility The evaluation of relationship can be referred to the following criteria: • Reasonable possibility: There are facts or evidences indicating the correlation between the investigational drug and AE, possibly based on but not limited to the following information: - The occurrence of the event is temporally related with the exposure of the investigational drug; - A known drug profile of the same pharmacological class of investigational drug may possibly result in such an event; - The event is relieved after the investigational drug is discontinued or its dose is reduced; - The event reoccurs if the investigational drug was reintroduced after having been stopped; - Biological potential; • No reasonable possibility: There are no facts or evidences indicating that the investigational drug is related with AE, possibly based on but not limited to the following information: - The event may be attributed to concomitant medications; - The event may be attributed to existing disease/ clinical condition; - The event may be attributed to a non-investigational drug; - The occurrence of the event is not associated with administration of the investigational drug rationally and temporally; - The event is an expected reaction in the target disease and/or population; - Dechallenge/Rechallenge is negative;
Page 66/ Section 8.2.1.7 Time Period and		Added text:

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Frequency of Detecting AEs and SAEs/ Ln 29						All AEs should be followed up, and follow-up information are recorded in the source documents and eCRF. For any AE unresolved after the end of the study, the investigator will continue to follow up and record the information in the source documents. The sponsor retains the right to request additional information for any subject with ongoing AE/SAE at the end of the study, if judged necessary.				
Page 67/ Table		Initial Reports		Follow-up Information on a Previous Report			Initial Reports		Follow-up Information on a Previous Report	
	Type of Event	Timeframe	Documents	Timeframe	Documents	Type of Event	Timeframe	Documents	Timeframe	Documents
	Liver chemistry abnormalities:					Liver chemistry abnormalities:				
	ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN (or ALT or AST $\geq 3 \times$ ULN and INR > 1.5 , if INR measured) ³	24 hours ¹	SAE data collection tool. ~~Liver event CRF and liver imaging and/or biopsy CRFs if applicable~~ ²	24 hours	Updated SAE data collection tool. ~~Updated liver event CRF~~ ²	ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN (or ALT or AST $\geq 3 \times$ ULN and INR > 1.5 , if INR measured) ²	24 hours ¹	SAE data collection tool.	24 hours	Updated SAE data collection tool.
	ALT or AST $\geq 5 \times$ ULN; ALT or AST $\geq 3 \times$ ULN with hepatitis or rash or $3 \times$ ULN ≥ 4 weeks	24 hours ¹	~~Liver event CRF~~ ²	24 hours	Updated liver event CRF ²	ALT or AST $\geq 5 \times$ ULN; ALT or AST $\geq 3 \times$ ULN with hepatitis or rash or $3 \times$ ULN ≥ 4 weeks	24 hours ¹	SAE data collection tool.	24 hours	Updated SAE data collection tool.

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	ALT or AST $\geq 3 \times$ ULN and $< 5 \times$ ULN and bilirubin $< 2 \times$ ULN	24 hours ¹	~~Liver event~~ ~~CRF~~ ² does not need completing unless elevations persist for 4 weeks or patient cannot be monitored weekly for 4 weeks ²			ALT or AST $\geq 3 \times$ ULN and $< 5 \times$ ULN and bilirubin $< 2 \times$ ULN	24 hours ¹	SAE data collection tool is not needed unless elevations persist for 4 weeks or patient cannot be monitored weekly for 4 weeks		
Page 67/ Section 8.2.1.8 Prompt Reporting of SAEs and Other Events/ Ln 4	2. Liver event documents (ie, Liver Event CRF and Liver Imaging CRF and/or Liver Biopsy CRF, as applicable) should be completed as soon as possible.					Footnote deleted				
Page 70/ Table 9. footnote/ Ln 15						Added footnote “2” to CA-125 test: 2. All CA-125 assessments will be performed by the central lab.				
Page 70/ Section 8.2.7 Clinical Laboratory Assessments/ Ln 16						Added text: All screening tests will be performed by the central lab in the US, or local labs in China (except 1,5-anhydroglucitol, insulin and CA-125 tests in China, which will be performed by the central lab).				
Page 70/ Section 8.2.7 Clinical Laboratory Assessments/ Ln 18	These clinical laboratory tests will be performed at the laboratory facilities associated with the investigational site, unless the facility does not fulfill the protocol requirement for the laboratory tests and at the central lab in the United States of America.					All clinical laboratory tests (excluding CA-125), starting from C1D1, will be performed at laboratory facilities approved by the investigational site.				
Page 78/ Ln 8	The whole section 8.3.6 Efficacy Assessment Incorporating RECIST 1.1 and GCIG CA-125 Criteria was deleted.					Section deleted				
Page 78/ Ln 8	Table 11. Best Overall Response in Patients with Measurable Disease and who are also Evaluable by CA 125					Table 11 deleted				

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Page 78/ Ln 8	Table 12. Definition of Progression per GCIG Criteria (RECIST 1.1 and CA-125)	Table 12 deleted
Page 78/ Section 8.4 Pharmacokinetics/ Ln 22		Added text: 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).
Page 78/ Section 8.4 Pharmacokinetics/ Ln 24	Each PK sample should be collected within $\pm 10\%$ of the planned time relative to the dose administered (ie, time zero) to the patient on serial PK days.	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.
Page 81/ 10.1 Hypotheses/ Ln 16	... the study population treated with the combination therapy of afuresertib and weekly paclitaxel is expected to have an improved PFS of 6.5 months...	... the study population treated with the combination therapy of afuresertib and weekly paclitaxel is expected to have an improved median PFS , i.e., 6.5 months...
Page 81/ Ln 19	$H_0: PFS_{comb} \leq PFS_{ctrl}$ versus $H_a: PFS_{comb} > PFS_{ctrl}$.	$H_0: PFS_{comb} = PFS_{ctrl}$ vs $H_a: PFS_{comb} \neq PFS_{ctrl}$.
Page 81/ Section 10.2 Sample Size Determination/ Ln 22	Previous studies have shown that PROC patients have a median PFS of around 3.5 months with weekly paclitaxel after 1 to 3 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed.	Previous studies have shown that PROC patients have a median PFS of around 3.5 months with weekly paclitaxel after 1 to 5 prior chemotherapies including no more than one chemotherapy after PROC was diagnosed.
Page 81/ Section 10.2 Sample Size Determination/ Ln 24	The combination therapy is expected to result in an estimated median PFS of 6.5 months, i.e. a 46% reduction of the disease progression risk.	The combination therapy is expected to result in an estimated median PFS, i.e., 6.5 months, corresponding to a 46% reduction of the disease progression risk.
Page 81/ Section 10.2 Sample Size Determination/ Ln 25	In the primary analysis, PFS of patients will be compared between the patients treated with the combination therapy and the monotherapy of paclitaxel using the unstratified log rank test.	Text deleted
Page 81/ Section 10.2 Sample Size Determination/ Ln 26	With the one-sided type I error rate controlled at 0.025, a total of 105 events are needed to provide about 85% statistical power to test the difference between the 2 therapies.	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.
Page 81/ Section 10.2 Sample Size Determination/ Ln 32	The primary statistical analysis will be based on a stratified log-rank test using the stratification variables (with exception of site) at randomization in the model. The hazard ratio and 95% CI will be calculated based on a stratified Cox proportional hazards model using	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.

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	the same stratification variables (with exception of site) at randomization.	
Page 82 Ln 3	The final analysis including all data will be conducted at the end of the study as defined in Section 5.1.4.	The final OS analysis including all data will be conducted at the end of the study as defined in Section 5.1.4.
Page 82/ Section 10.3.1 Analysis Sets/ Ln 13	The Per-Protocol Set (PPS) consists of all patients in the FAS who are in compliance with the protocol in the following ways: • diagnosis corresponds to that defined in inclusion criteria • stage of disease corresponds to that defined in inclusion criteria • prior treatment corresponds to that defined in inclusion criteria Patients who have major protocol deviations may be excluded from the PPS based on a study team review of all protocol deviations, which will be conducted before database lock.	Text deleted
Page 82/ Section 10.3.2 Interim Analysis/ Ln 17	The interim analysis of all secondary endpoints will be performed by the time of primary data analysis. Hypothesis testing of OS will be conducted if improvement of PFS demonstrates statistical significance (refer to Section 10.3.3.3.2).	The interim analysis of OS will be performed by the time of primary data analysis. Hypothesis testing of OS will be conducted if improvement of PFS demonstrates statistical significance (for more multiplicity handling , refer to Section 10.3.3.3.2).
Page 82/ Section 10.3.3 Key Elements of Analysis Plan/ Ln 30	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.	Text deleted
Page 83/ Section 10.3.3.3.1 Primary analysis/ Ln 32	The primary statistical analysis will be based on a stratified log-rank test using the stratification variables (with exception of site) at randomization in the model. The hazard ratio (HR) and 95% CI will be calculated based on a stratified Cox proportional hazards model using the same stratification variables (with exception of site) at randomization.	The primary statistical analysis will be based on an unstratified log-rank test. The hazard ratio (HR) and 95% CI will be calculated based on an unstratified Cox proportional hazards model.
Page 84/ Section 10.3.3.3.1 Primary analysis/ Ln 3	These analyses on PFS will be performed for the FAS as primary analysis and for PPS as secondary analysis.	These analyses on PFS will be performed for the FAS as primary analysis.
Page 84/ Section 10.3.3.3.1 Primary analysis/ Ln 4	Additional sensitivity analyses for the primary endpoint PFS based on tumor assessments will be performed using different censoring rules as proposed in the Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics by FDA (2007).	Additional sensitivity analyses for the primary endpoint PFS based on tumor assessments will be performed.

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Page 84/ Analysis of OS/ Ln 10	The median OS will be provided along with the 95% CI. The HR and 95% CI will be calculated based on a stratified Cox proportional hazards model using the same stratification variables (with exception of site) at randomization.	The median OS will be provided along with the 95% CI. The HR and 95% CI will be calculated based on an unstratified Cox proportional hazards model.
Page 84/ Analysis of OS/ Ln 12	Although the study is not powered for the secondary endpoint OS, two-sided stratified log-rank test will be performed ...	Although the study is not powered for the secondary endpoint OS, two-sided unstratified log-rank test will be performed ...
Page 84/ Analysis of OS/ Ln 18	The O'Brien-Fleming type alpha-spending function will be applied ...	The O'Brien-Fleming type Lan -Demets alpha-spending function will be applied ...
Page 84/ Analysis of the other secondary endpoints/ Ln 25	The Clopper-Pearson method will be used to provide an estimation of ORR, DCR and CA-125 response rates with 95% CIs and the treatment differences and 95% CIs for these endpoints.	The Clopper-Pearson method will be used to provide an estimation of ORR, DCR and CA-125 response rates with 95% CIs and the wald test will be used for treatment differences with 95% CIs for these endpoints.
Page 84/ Analysis of the other secondary endpoints/ Ln 28	The HR and 95% CI will be calculated based on an unstratified Cox proportional hazards model using the same stratification variables (with exception of site) at randomization.	The HR and 95% CI will be calculated based on an unstratified Cox proportional hazards model.
Page 85/ Ln 22	Laboratory data will also be displayed by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).	Text deleted
Page 92/ References		Added: ⁴³ Alison Davis, Anna V. Tinker, Michael Friedlander. "Platinum resistant" ovarian cancer: What is it, who to treat and how to measure benefit? Gynecologic Oncology 2014, 133(3):624-631.
End of Summary		

Summary of Changes

From Version 5.0 to Version 6.0

Page/ Section/ Lines in new version	Version 5.0	Version 6.0	Brief Rationale
Document header		Added “ver.6.0”	Indicate version
Title page/ Document version number	5.0	6.0	Update
Title page/ Effective date	20 September 2021	23 January 2023	Update
Title page/ Authors	Angela Castagna, BA: Clinical Operation Lead	Xiaoyu Wang, MD, PhD: Medical Director	Update
Title page	Copyright 2021 Laekna Limited.	Copyright 2023 Laekna Limited.	Update
Title page/ Sponsor Signatory/ Date	I, the undersigned, have reviewed and approved version 5.0 of the clinical study protocol with the date of 20 September 2021.	I, the undersigned, have reviewed and approved version 6.0 of the clinical study protocol with the date of 23 January 2023.	Update
Page 4 List of study personnel	Removed Vivian Liu	Added Kris Ma and Jing Qu	Update personnel
Page 17 and 30/ Exploratory Objectives and Endpoints		Added Exploratory objectives “To conduct exploratory metabolite analysis of afuresertib in PK samples remaining after quantification of afuresertib / paclitaxel” Added Exploratory endpoints “Metabolite analysis and / or quantification will be described in a report separately from the CSR.”	Add metabolite analysis as exploratory objective
Page 31/ Sec 4.1	“paclitaxel 80 mg/m ² intravenous (IV) infusion over 1 hour”	“paclitaxel 80 mg/m ² intravenous (IV) infusion in 1 hour”	Clarify paclitaxel infusion duration
Page 33/ Sec 5.1.2 Inclusion criteria #2		Added “(Note: Core biopsy should not be performed within 7 days prior to Study Day 1.)”	Add to reduce risk of GI perforation
Page 34/ Sec 5.1.3 Exclusion criteria #4	“Uncontrolled ascites”	Added “Uncontrolled ascites, defined as “patients who presented with > 500 ml of ascites at screening; or has required paracentesis in the 3 months prior to screening, and/or is anticipated to require paracentesis during the study, to remove > 500 mL of ascites on a regular basis”.	Further define “uncontrolled ascites” to reduce risk of GI perforation
Page 35/ Sec 5.1.3 Exclusion criteria #11		Added “In addition, patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis should also be excluded.”	Add to reduce risk of GI perforation

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Page 35/ Sec 5.1.3 Exclusion criteria #17	“Had a major surgery $\leq$ 30 days prior to first study treatment at Cycle 1 Day 1.”	Changed to “Had a major non-abdominal surgery $\leq$ 30 days, or a major abdominal surgery within 8 weeks prior to first study treatment at Cycle 1 Day 1. In addition, patients who have anticipated major surgical procedures during the study, including but not limited to abdominal surgery (laparotomy or laparoscopy) prior to disease progression, such as colostomy or enterostomy reversal should also be excluded.”	Add to reduce risk of GI perforation
Page 36/ Sec 5.1.3 Exclusion criteria #23		Added new criterion #23 “Patients with higher risk of gastrointestinal perforation/fistula, including but not limited to the following conditions: • Presence of $\geq$ CTCAE Grade 2 weight loss over the 3 months prior to screening, or who had anorexia; • Evidence of direct bowel involvement with tumor: rectovaginal nodularity; CT evidence of direct bowel involvement; • Patients with serious non-healing wound or ulcer, with history of abdominal fistula or gastrointestinal perforation, or with intra-abdominal abscess within 28 days prior to screening. • Patients with prior history of gastrointestinal disease or pre-existing GI symptoms, such as diarrhea or vomiting $\geq$ grade 2, GI obstruction, GERD, inflammatory bowel disease, diverticular disease, etc. The presence of abdominal pain should be further evaluated for risk of GI perforation.	Add to reduce risk of GI perforation
Page 40/ Sec 6.7/ Ln 1	“Patients will be withdrawn from the study if any of the following occurs”	Changed to “Patients will be withdrawn from the study treatment if any of the following occurs”	Clarify “discontinuation

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			of study treatment”
Page 40/ Sec 6.7/ Paragraph 3	“All patients who discontinue study treatment for a reason other than PD, death, or withdrawal of consent for further treatment and data collection will have the end of treatment (EOT) visit 30 days (±7 days) after the last dose.”	Changed to “All patients who discontinue study treatment for a reason other than PD, death, or withdrawal of consent for further treatment and data collection will have the end-of-treatment (EOT) visit within 30 days (±7 days) after the last dose.”	Clarify EOT visit timeframe
Page 41/ Sec 6.7/ Paragraph 1		Added “ Patients have the right to discontinue the study at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study at any time, though efforts should be made to retain patient in the study if there is no conflicting health and safety concerns. Reasons for withdrawal from the study may include, but are not limited to, the following: • Death • Patient withdrawal of consent for further treatment or data collection • Lost to follow-up • Study termination or site closure • Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor”	Add reasons for withdrawal from of study
Page 41/ Sec 6.8/ Paragraph 2	“A maximum of two dose level modifications per study drug are allowed during the study.”	Changed to “A maximum of two dose level modifications for afuresertib are allowed during the study. There is no limit on dose modification of paclitaxel. ”	Clarify that no limit on paclitaxel dose modification
Page 43/ Table 3. Dose Modification Guidance	“Diarrhea or Fatigue or Skin rash”	Changed to “Fatigue or Skin rash”	Make diarrhea a separate item
Page 43/ Table 3. Dose Modification Guidance		Added the following:	Add dose modification guidance for diarrhea as a

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		Diarrhea	Grade 1	Consider dose reduction to 125 mg D1-4, Q7D. Consider to return to 125 mg QD if resolved to baseline*.	Consider dose reduction to 50 mg/m ² , IV weekly. Consider to return to 80 mg/m ² , if resolved to baseline.	separate item to reduce the risk of GI perforation
			Grade ≥ 2	Hold afuresertib until the AE reduces to grade 1; Then resume afuresertib 125 mg, D1-4, Q7D for 7-14 days; If tolerated well, return to 125 mg QD*. *Patient with grade 1 diarrhea can be considered to return to 125 mg QD if no other risk factors of GI perforation based on investigator's clinical assessment.	Hold paclitaxel until the AE reduces to grade 1; Then resume paclitaxel 50 mg/m ² , IV weekly for 1-2 weeks; If tolerated well, return to 80 mg/m ² .	

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Page 49/ Sec 6.9.1 Supportive Care for Diarrhea	“• For grade 1 diarrhea, consider afuresertib dose reduction from 125 mg QD to 125 mg D1-4, Q7D. Consider to return to 125 mg QD if diarrhea resolves to baseline. • For grade 2 diarrhea, temporarily discontinue afuresertib until diarrhea resolves to grade 1.”	Changed to “Modify doses of study drugs per Table 3 “Dose Modification Guidance” - For grade 1 diarrhea, consider afuresertib dose reduction from 125 mg QD to 125 mg D1-4, Q7D and paclitaxel from 80 mg/m² to 50 mg/m² weekly. Consider to return to study specified doses if diarrhea resolves to baseline*. - For grade ≥ 2 diarrhea, temporarily hold afuresertib and paclitaxel until diarrhea resolves to grade 1. Then resume afuresertib 125 mg, D1-4, Q7D for 7-14 days and paclitaxel 50 mg/m², IV weekly for 1-2 weeks. If tolerated well, return to study specified doses*. *Patient with grade 1 diarrhea can be considered to return to 125 mg QD if no other risk factors of GI perforation based on investigator’s clinical assessment.”	Changed to be consistent with newly added dose modification guidance for diarrhea in Table 3 to reduce the risk of GI perforation
Page 53/ Sec 7.3.1/Paragraph 2	“Based on in vitro information, co-administration of afuresertib and medications that are a sensitive substrate of CYP2C8 with low therapeutic index will be used with caution”	Changed to “Based on in vitro information, co-administration of afuresertib and medications that are a sensitive substrate of CYP2C8 without low therapeutic index will be used with caution”	Correct typographical error
Page 61/ Table 8 Time and Events Table/ Footnote #3	“The End of Treatment visit should be 30 ($\pm$ 7) days from the last dose of study drug.”	Changed to “The End-of-Treatment visit should be within 30 days ($\pm$ 7 days) from the last dose of study drug.”	Clarify EOT visit timeframe
Page 61/ Table 8 Time and Events Table/ Footnote #15	“PK sampling time points are described below (see Section 4.1.1 for further details).”	Changed to “15. PK sampling time points are described below (see Section 4.1.1 and 8.4.1 for further details).”	Changed to reflect changes made in Section 8.4.1 for clarity.
Page 62/ Table 8 Time and Events Table/ Footnote #15		Added “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-	Added footnote regarding PK sample collection to be consistent with

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		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.”	changes made in Section 8.4.1 for clarification
Page 62/ Table 8 Time and Events Table/ Footnote #17	“Archival tumor tissue collection is required to be collected within 1 year before the screening visit is preferred.	Changed to “Archival tumor tissue collected within 1 year before the screening visit is preferred, but older samples are acceptable.”	Correct typographical error and add clarification to be consistent with Inclusion criterion #2
Page 72/ Sec 8.3/ Paragraph 1	“Blind Imaging Central Review”	Changed to “Blind Independent central Review”	Correct typographical error
Page 79/ Sec 8.4 Paragraph 1/		Added “PK plasma samples from Arm 1 may also be used for exploratory metabolite analysis.”	Add to be consistent with new exploratory objective
Page 80/ Sec 8.4.1/ Paragraph 2	“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). Each post-dose PK sample should be collected within $\pm 10\%$	Added “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 time-points after the start of the paclitaxel infusion. The 24-hours timepoint are pre-	Clarify PK sample timepoints and paclitaxel infusion duration for PK study

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	time window of the planned timepoints in reference to the starting time of paclitaxel IV infusion on serial PK days.”	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 $\pm$ 6 minutes. If the paclitaxel infusion time is prolonged (> 1 hour $\pm$ 6 minutes) due to infusion reaction, the 1-hour pose-dose PK sample should be collected immediately at the end of the infusion.”	
Page 83/ Sec 10.3.1/ Paragraph 2	“The Safety Set includes all patients from the FAS who have received at least one dose of study treatment ~~and had at least one valid post-baseline safety assessment~~ . Safety Set will be used for all safety analyses.”	“The Safety Set 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.”	Redefine Safety set
Page 83/ Sec 10.3.1	“The PK Analysis Set (PAS) consists of all patients set who have at least one sample providing evaluable PK data. ”	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 log ₁₀ /linear scale for the PAS. 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.	Define PK analysis set in detail

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		Summary statistics (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.	
Page 84/Sec 10.3.3.2.1	“The FAS will be used.”	Changed to “The Safety Set will be used.”	Correct dataset
Page 85/ Sec 10.3.3.2.3/ Paragraph 2	“Study medication compliance will be assessed by relative dose intensity and ~~the incidence of dose reduction, overdosing and dose interruption due to reasons other than per protocol.~~ ”	Changed to “Study medication compliance will be assessed by relative dose intensity and compliance of afuresertib. ”	Simplify for clarity
Page 86/ Sec 10.3.3.4.2/ Paragraph 2	“For each laboratory test (eg, hematology, biochemistry, etc.), a listing of laboratory values will be provided by laboratory parameter, patient and treatment arm. ~~The frequency of notable laboratory abnormalities will be displayed by parameter and visit. Similarly, the frequency of all laboratory abnormalities will be displayed by parameter, and worst CTCAE grade experienced. A separate listing will display notable laboratory abnormalities (ie, newly occurring CTCAE grade 3 or 4 laboratory toxicities).~~ ”	“For each laboratory test (eg, hematology, biochemistry, etc.), a listing of laboratory values will be provided by laboratory parameter, patient and treatment arm.”	Adjust safety analysis data output
Page 86/Sec 10.3.3.4.3	“The results of scheduled assessments of body weight, vital signs, 12-lead ECG, ~~and ECOG performance status~~ will be summarized.”	Changed to “The results of scheduled assessments of body weight, vital signs, and 12-lead ECG will be summarized.	Adjust safety analysis data output
Page 94/Appendix 1	“CL _{cr} (mL/min) = Q × (140-age[yr]) × actual body weight [kg] * 72 × serum creatinine [mg/dL]	Changed “multiplication operator” to “division operator” “CL _{cr} (mL/min) = Q × (140-age[yr]) × actual body weight [kg] / (72 × serum creatinine [mg/dL])”	Correct typographical errors

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Other typographical errors across the document may not be listed individually.	“aEs”	“AEs”	Correct typographical errors
End of Summary			