PiSARRO-R: p53 Suppressor Activation in Platinum-Resistant High Grade Serous Ovarian Cancer, a Phase II Study of Systemic Pegylated Liposomal Doxorubicin Chemotherapy With APR-246

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PROTOCOL APPROVAL PAGE

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INVESTIGATOR'S STATEMENT

PiSARRO-R: p53 Suppressor Activation in Platinum-Resistant High Grade Serous Ovarian Cancer, a Phase II Study of Systemic Pegylated Liposomal Doxorubicin Chemotherapy With APR-246

This page will be institute specific and should list the investigator that will sign-off the separate protocol agreement.

1. I agree to conduct this study as outlined in the protocol.
2. I understand that this study will not be initiated without approval of the appropriate Independent Ethics Committee (IEC), and that all administrative requirements of the governing body of the Institution will be complied with fully.
3. Informed written consent will be obtained from all participating patients in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013).
4. I will enroll patients who meet the protocol criteria for entry.
5. I understand that my signature on each completed Electronic Case Report Form indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration, a Competent Authority of the European Union or another Regulatory Authority.

Investigator Signature

Name: _____

Title: _____

Signature _____

Date _____

Institution name and address: _____

_____

_____

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CLINICAL STUDY SYNOPSIS

Name of Sponsor: Aprea Therapeutics AB Nobels väg 3 SE-171 65 Solna Sweden	**Study Phase:** Phase II
Name of Finished Product: APR-246, concentrate for solution for infusion	
Name of Active Ingredient: 2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo [2,2,2] octan-3-one	
Title of the Study: PiSARRO-R: p53 Suppressor Activation in Platinum-Resistant High Grade Serous Ovarian Cancer, a Phase II Study of Systemic Pegylated Liposomal Doxorubicin Chemotherapy With APR-246	
Investigators and Study Centers: Please see Study Operations Manual	
Publication (Reference): To be confirmed	
Clinical Phases: Phase II	
Study Design and Number of Patients: This study is an open-label, multicenter phase II study to evaluate the preliminary efficacy of APR-246 with systemic pegylated liposomal doxorubicin (PLD) chemotherapy in TP53-mutated high grade serous ovarian cancer (HGSOC) in patients with recurrent disease occurring between 4 weeks and 6 months after a preceding platinum-based treatment (platinum-resistant patients). Different APR-246 infusion times will be explored. The Main Study will assess the standard 6 hour APR-246 infusion whilst the Sub-Study will explore shorter infusions (3 or 4 hour). At least 25 evaluable patients will receive the standard 6 hour APR-246 infusion. Up to 25 additional patients may be enrolled in a Sub-Study exploring shorter APR-246 infusion durations (3 or 4 hours). The Sub-Study will start enrollment after at least 6 patients have received the standard 6 hour infusion in the Main Study. The Sub-Study will be conducted in parallel with the Main Study. A safety review committee (SRC) will evaluate the first 6 patients who receive the standard 6 hour infusion and the first 6 patients in the Sub-Study, to determine whether further patients can be lled and receive the same APR-246 infusion duration, at the same dose.	
Objectives, Endpoints and Study Treatment: **Main Study Objectives:** **Primary Objectives:** • To assess the preliminary efficacy of APR-246 with PLD chemotherapy in patients with platinum-resistant HGSOC with mutated TP53 **Secondary Objectives:** • To evaluate the pharmacokinetics (PK) of APR-246 when administered with PLD chemotherapy • To evaluate cardiac safety of APR-246 when administered with PLD chemotherapy • To assess the safety and tolerability of APR-246 with PLD chemotherapy in patients with platinum-resistant HGSOC with mutated TP53	

- To assess:
  - Duration of response (complete or partial response)
  - Progression-free survival (PFS) by assessment of cancer antigen 125 (CA-125)
  - PFS by RECIST 1.1
- To evaluate potential biomarkers and tumor activity based on CA-125
  To assess the biological activity in tumor and surrogate tissues

Main Study Endpoints:

Primary Endpoints:

- Overall response rate according to RECIST 1.1

Secondary Endpoints:

- PFS rate, defined as the time from registration to the time of disease progression or relapse (according to RECIST 1.1 only) or death, or the date of last tumor assessment without any such event (censored observation)
- PK profile of APR-246 and concentration in plasma
- Cardiac profile of APR-246 and concentration of PLD
- The safety profile (adverse events [AEs], laboratory assessments, physical findings and biomarkers) of APR-246 and PLD chemotherapy
- Duration of response (complete or partial response)
- Progression-free survival (PFS) by assessment of CA-125
- Evaluation of potential biomarkers
- Biological activity in tumor and surrogate tissues

Objectives, Endpoints and Study Treatment:

Sub-study Objectives: Same as Main Study Objectives, except safety and tolerability, in addition to preliminary efficacy, are Primary Objectives.

Sub-Study Primary Endpoints: The safety profile (adverse events [AEs], laboratory assessments, physical findings and biomarkers) of APR-246 with a shorter infusion and PLD chemotherapy; overall response rate according to RECIST 1.1.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Archived sections from the original formalin fixed paraffin embedded sample reviewed by a gynecological pathologist confirming HGSOC, high grade serous peritoneal cancer or primary fallopian tube cancer and positive immunohistochemistry staining for p53 assessed according to the local methodology (as detailed in the laboratory manual). Cases that do not show p53 staining will not be included.
2. Disease progression between 4 weeks and 6 months after the last platinum-based treatment was administered.
3. At least a single (RECIST 1.1) measurable lesion.
4. Adequate organ function prior to registration:
   a) Bone marrow reserve
      - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L

- Platelets ≥ 100 x 10^9/L
- Hemoglobin ≥ 9 g/dL

b) Hepatic
- Total bilirubin level < 1.5 x ULN without hepatic metastasis, and < 4 x ULN with hepatic metastasis
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x ULN without hepatic metastasis, and < 4 x ULN with hepatic metastasis

c) Renal
- Calculated creatinine clearance > 30 mL/min calculated per local practice

d) Electrolytes
- Potassium within institutional normal ranges.

5. Toxicities from previous cancer therapies (excluding alopecia) must have recovered to grade 1 (defined by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.0). Chronic stable grade 2 peripheral neuropathy secondary to neurotoxicity from prior therapies may be considered on a case by case basis by the Principal Investigator.
6. If of childbearing potential, negative pretreatment serum pregnancy test.
7. If of childbearing potential, willing to use an effective form of contraception (see below) during chemotherapy treatment and for at least 6 months thereafter. Such methods include the following (if using hormonal contraception, this method must be supplemented with a barrier method, preferably male condom):
   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - oral
     - intravaginal
     - transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation:
     - oral
     - injectable
     - implantable
   - intrauterine device (IUD)
   - intrauterine hormone-releasing system (IUS)
   - bilateral tubal occlusion
   - vasectomized partner
   - true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Appendix I).
9. ≥ 18 years of age.
10. Signed informed consent.

Exclusion Criteria:

1. Prior exposure to cumulative doses of doxorubicin >400 mg/m^2 or epirubicin >720 mg/m^2.
2. Confirmed cardiac history of any of the following:
   a) A myocardial infarct within 6 months prior to registration,

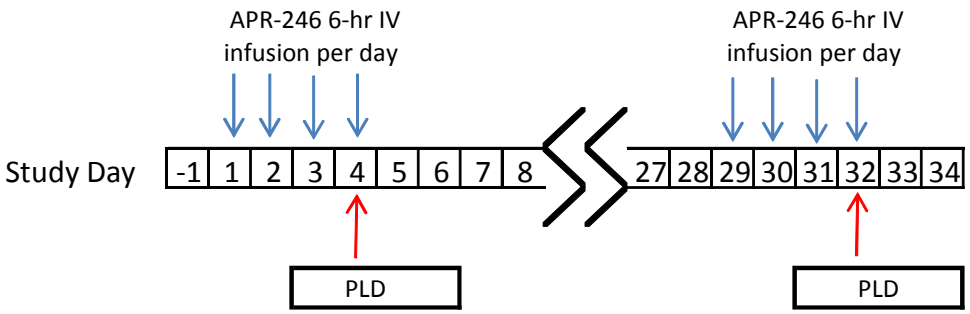
b) New York Heart Association Class II or worse heart failure (Appendix II)
c) A history of familial long QT syndrome
d) Clinically significant pericardial disease
e) Electrocardiographic evidence of acute ischemia
f) Symptomatic atrial or ventricular arrhythmias not controlled by medications
g) QTc ≥ 480 msec calculated from a single electrocardiogram (ECG) reading or a mean of three ECG readings using Fridericia's correction (QTcF = QT/RR0.33)
h) Bradycardia (< 40 bpm)
i) Left ventricular ejection fraction (LVEF) < the institution lower limit of normal as assessed by echocardiogram.

3. Major abdominal surgery or peritonitis within 6 weeks prior to study treatment.
4. Unresolved bowel obstruction, subocclusive disease or the presence of brain metastases.
5. Hypersensitivity to PLD or to any of the excipients.
6. Unable to undergo imaging by either computed tomography (CT) scan or magnetic resonance imaging (MRI).
7. Evidence of any other medical conditions (such as psychiatric illness, infectious diseases, neurological conditions, physical examination or laboratory findings) that may interfere with the planned treatment, affect patient compliance or place the patient at high risk from treatment related complications.
8. Breast feeding.
9. Concurrent malignancy requiring therapy (excluding non-invasive carcinoma or carcinoma in situ).
10. Known HIV positive status, active hepatitis B or C status.
11. Is taking any concurrent (or within 4 weeks prior to registration) anti-cancer therapy, immunotherapy, radiotherapy, biological, or ancillary anti-cancer therapy, or any therapy that is considered to be investigational (i.e., used for non-approved indications(s) and in the context of a research investigation). Supportive care measures are allowed. Palliative limited radiation therapy for pain reduction is allowed.

Test Product, Dose and Mode of Administration:

Main Study:

Patients will receive a fixed dose of 4.5 g APR-246 (1.5 g of the dose during first 45 minutes followed by 3 g of the dose during 5 hours 15 minutes) on Days 1 to 4 with PLD 40 mg/m^2 on Day 4. The PLD administration to be given on Day 4 only should commence 2 hours after the start of the APR-246 infusion. Similarly for the following 28-day cycles, APR-246 will be administered on Days 1 to 4 with the PLD infusion on Day 4 starting 2 hours after the start of the APR-246 infusion. In all cycles, APR-246 will be administered as a 6-hour infusion.



Test Product, Dose and Mode of Administration:

Sub-Study:
Starting within 28 days of registration, patients will receive a fixed dose of 4.5 g APR-246 in a 2-step infusion, starting with a loading dose given during first 45 minutes followed by slower infusion of the remainder of the dose, during 2 hours 15 minutes on Days 1 to 4, with PLD 40 mg/m^2 on Day 4. The PLD administration to be given on Day 4 only should commence 2 hours after the start of the APR-246 infusion.

Other infusion durations and doses that may be explored in the Sub-Study are 4 hour 4.5 g, or 4 hour 3.7 g.

Duration of Treatment:
Patients will receive 28-day cycles of PLD chemotherapy with APR-246. Patients may continue to receive APR-246 with PLD for as long as in the Investigator's opinion they are benefiting from treatment and in the absence of disease progression and unacceptable toxicity. After the tenth 28-day cycle, data from assessments conducted within each treatment cycle will no longer be collected, but patients may continue to receive treatment after confirmation from the sponsor.

Reference Therapy, Dose and Mode of Administration:
Not applicable

Criteria for Evaluation:

Efficacy:
Patients with measurable disease will be assessed using RECIST 1.1 criteria.

Safety:
AEs will be collected throughout the study, from informed consent until 30 days after the last administration of study treatment. AEs will be graded according to NCI CTCAE version 4.0. Serious adverse events (SAEs) will be reported according to Directive 2001/20/EC and 2005/28/EC and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Main Study Sample Size Calculation:
This study uses a two-stage design to test the null hypothesis is that the true response rate of APR-246 in combination with PLD is ≤10% versus the alternative that the true response rate is ≥30% in patients with platinum-resistant, TP53-mutated HGSOC. In the first stage, 16 patients will be assessed for response; if ≤1 response is seen in these 16 patients the study will be curtailed for futility. Otherwise the study will continue and a further 9 patients will be entered, for a total of 25 evaluable patients. If ≥5 responses are observed in these 25 patients, the null hypothesis will be rejected in favor of the alternative. This design provides 90.3% power and a 1-sided alpha of 9.5%.

Sub-Study Sample Size:
At one of the shorter infusion levels (3 hr 4.5 g, 4 hr 4.5 g, or 4 hr 3.7 g) if there are 0 or 1 out of 6 patients with DLTs across the first patients, then an additional 8 patients will be treated for an initial total of N=14. If 0 or 1 out of 14 responses are seen, then recruitment will cease. If 2 or more out of 14 responses are seen, a further 11 patients will be recruited for a total of N=25. Observance of 5/25 responses will result in rejection of the null hypothesis. The design carries 89% power and a 1-sided type I error of 9.1% to test the null hypothesis that the true response rate is ≤10% vs the alternative that the true response rate is 30%.

LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
CA	Competent Authority
CA-125	Cancer Antigen 125
CD	Candidate Drug
CLL	Chronic Lymphocytic Leukemia
Cmax	Maximal Plasma Concentration
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOC	Epithelial Ovarian Carcinoma
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HGSOC	High Grade Serous Ovarian Cancer
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IV	Intravenous
IWRS	Interactive Web Response System

LBM	Lean Body Mass
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	UK Medicine and Healthcare Products Regulatory Agency
MQ	Methylene Quinuclidinone
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
PARP	Poly (adenosine diphosphate [ADP]) Ribose Polymerase
PD	Progressive Disease
PFI	Platinum-free Interval
PFS	Progression-free Survival
PiSARRO-R	p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer-Resistant
PK	Pharmacokinetics
PLD	Pegylated Liposomal Doxorubicin
PR	Partial Response
PRIMA	p53 Reactivation and Induction of Massive Apoptosis
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SRC	Safety Review Committee
tid	Three Times Daily
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell Count

1.0 GENERAL INFORMATION

1.1 Protocol Number and Title of the Study

APR-486
PiSARRO-R: p53 Suppressor Activation in Platinum-Resistant High Grade Serous Ovarian Cancer, a Phase II Study of Systemic Pegylated Liposomal Doxorubicin Chemotherapy With APR-246

1.2 Sponsor

This study is being sponsored by Aprea Therapeutics AB.
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1.5 Safety Review Committee

After the first six patients have been enrolled in the Main Study, and after the first six patients are enrolled in the Sub-Study, a Safety Review Committee (SRC) will evaluate the safety, tolerability and all other data concerning the action of APR-246 to determine should the study proceed to complete enrollment, or should an alternative dose and/or schedule be explored. The SRC will consist of:

- Medical Monitor (Theradex®), who will chair the committee, or delegate
- Principal Investigator or delegate from each investigational site
- Medical Monitor (Aprea Therapeutics AB) or delegate

The Study Pharmacokineticist, Project Managers and other technical experts may also be invited as appropriate. If required, a SRC Remit document will define the exact membership and who should be present for decisions to be made.

The decisions and decision-making of the SRC on dose and duration of APR-246 infusion will be documented and provided to the investigators prior to dosing any new patients.

2.0 INTRODUCTION AND RATIONALE FOR THE STUDY

The purpose of this phase II study is to evaluate the preliminary safety and efficacy of different APR-246 infusion durations with systemic pegylated liposomal doxorubicin (PLD) chemotherapy in TP53-mutated high grade serous ovarian cancer (HGSOC) in patients with recurrent disease occurring between 4 weeks and 6 months after a preceding platinum-based treatment (platinum-resistant patients). The study will also determine PK variables for APR-246. Patients will receive APR-246 with PLD chemotherapy.

2.1 Background Information

2.1.1 General Information

Aprea Therapeutics AB was founded in 2003 by the inventors Klas Wiman, Galina Selivanova, Vladimir Bykov, Staffan Strömblad, Wenjie Bao and Natalia Issaeva together with Karolinska Innovations AB. The company is aiming to develop targeted, specific drugs for the treatment of cancer by restoration of p53 function.

The company has identified molecules that via p53-dependent pathways induce apoptosis in cancer cells with mutant or wild type p53. Aprea Therapeutics AB has since its inception confirmed the data in house and has screened for novel substances. The compound APR-246 has been selected as the company's first candidate drug (CD).

2.1.2 The p53 Protein and APR-246

p53 was discovered in 1979 as a cellular protein that forms a complex with the viral large T protein in SV40-infected cells. Later studies showed that p53 was a tumor suppressor which could inhibit cell growth and trigger cell death by apoptosis. TP53, the p53 gene is mutated in almost half of all human tumors. The p53 status of a tumor may have a strong impact on sensitivity to commonly used anticancer drugs and radiotherapy [1]. Thus, p53 is an important clinical marker and also a novel therapeutic target. In contrast to other tumor suppressor genes, TP53 is typically inactivated by single missense mutations, which is accompanied by loss of the remaining wild type allele. As a rule, mutant p53 proteins are deficient for specific DNA binding suggesting that DNA binding and transcriptional regulation of target genes are critical functions for p53-mediated tumor suppression [2].

The fact that TP53 is mutated in around 50% of human tumors, that mutant p53 protein usually accumulates at high levels, and that mutant p53-expressing tumors respond poorly to conventional therapy makes mutant p53 an attractive target for novel cancer therapy [3]. In hematological malignancies, between 5 and 20% of the patients carry a TP53 mutation in their malignant cell clone. However, for the current indication more than 95% of patients with HGSOC carry TP53 mutations [4].

Recent studies have demonstrated that restoration of p53 in p53-deficient murine tumors triggers rapid and efficient elimination of the tumor through cell cycle arrest, senescence and/or apoptosis [5]. This supports the idea that pharmacological reactivation of p53 should allow efficient elimination of tumors with minimal effects on normal cells.

The small molecule PRIMA-1 (p53 reactivation and induction of massive apoptosis-1; later denoted APR-017) was identified in a cellular screen for compounds that preferentially induce apoptosis in human tumor cells expressing exogenous mutant p53. Optimization of APR-017 resulted in the structural analogue APR-246, the IMP for this study. Treatment with APR-246 has been shown to restore sequence specific DNA binding, wild type conformation and transcriptional transactivation to mutant p53 protein. Furthermore, APR-246 has been shown to synergize with the DNA damaging anticancer agents, including platinum compounds and doxorubicin (see Investigator's Brochure [IB]).

2.2 Disease Background

Ovarian cancer is the sixth most commonly diagnosed cancer among women in the world, at over 60,000 cases per year, and causes more deaths per year than any other cancer of the female reproductive system [6]. Ovarian cancer has been of considerable interest to clinical cancer investigators due to the fact that it is among the most chemosensitive of all solid tumors [7]. The commonest histological subtype is HGSOC, which is the focus of this study.

First line management of HGSOC involves optimal debulking surgery and platinum/taxane combination chemotherapy. Although this often produces a radiological complete response, the majority of patients will subsequently relapse and eventually develop platinum resistance to which the patient will ultimately succumb. The 5-year survival rate remains poor at less than 40%. Thus, there is a need for improved treatment of relapsed ovarian cancer.

Patients are generally retreated at relapse with platinum-based combinations unless the cancer relapses within 6 months of previous platinum-based chemotherapy (previously referred to as 'platinum resistant'). Patients who relapse within this timescale have poor prognosis and are often resistant to multiple chemotherapeutic agents [8]. Single-agent therapies used to treat this subset of patients include weekly paclitaxel, PLD and topotecan. The response rate is in the 10–15% range and overall survival is approximately 12 months [9].

HGSOC accounts for approximately 70% of epithelial ovarian carcinoma in Europe and North America [10]. Mutant TP53 is a hallmark of HGSOC, resulting in deregulation of cell cycle checkpoints and uncontrolled tumor cell proliferation and thus represents a key driver event. Pathogenic TP53 mutations have been quoted as occurring in up to 96% of patients with HGSOC [4].

APR-246 has been shown to induce apoptosis and cell death in cancer cells with mutant or otherwise non-functional p53, and in addition to display strong synergistic anticancer effects in combination with several conventional chemotherapeutic drugs including platinum drugs and doxorubicin [11, 12].

2.3 Choice of Patient Population

The study population will include patients with TP53-mutated HGSOC whose cancer recurs more than 4 weeks and less than 6 months after their last administration of platinum-based chemotherapy and who, in the Investigator's opinion, are still suitable for chemotherapy. Relapse should be verified radiologically.

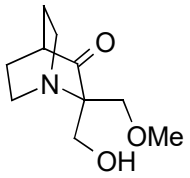
On the basis of preliminary efficacy data from study APR-407 (Section 2.7.1), which recruited patients relapsing between 6 and 24 months after preceding platinum-based chemotherapy, there is a strong scientific rationale to explore whether similar initial clinical responses could be observed in patients who progress 1-6 months after a preceding platinum regime.

2.4 Investigational Medicinal Product

The investigational medicinal product (IMP), APR-246 concentrate for solution for infusion 150 mg/mL, contains APR-246, 2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo [2,2,2] octan-3-one, is also called PRIMA-1^{Met} in the literature, where PRIMA is an acronym for p53 reactivation and induction of massive apoptosis (see IB).

The APR-246 compound has a molecular weight of 199.24 g/mol, is a racemic mixture and is isolated as a white powder. The structure of APR-246 can be seen in Figure 1 below.

Figure 1. Structure of APR-246



The IMP should be stored at 2-8°C. The IMP is a concentrated solution which should be diluted with sterile 0.9% sodium chloride solution for infusion before administration. The solution for infusion should be prepared with the prescribed dosage for each patient in accordance with the protocol and separate technical instruction. After preparation of the ready-to-use solution for infusion, the pH of the solution will range from slightly above 4 up to approximately 4.8, depending on dosage. The infusion will be slightly hypertonic. The prepared APR-246 study product is to be stored at not more than 25°C. The infusion to the patient should be finalized within 24 hours from the time of preparation.

APR-246 is a prodrug that is converted to the active compound MQ, responsible for the anticancer effects of APR-246. APR-246 in physiological conditions is converted to MQ, which has been

shown to bind to cysteines in mutant unfolded p53, stabilising the protein in a functional wild type conformation.

2.5 Preclinical Studies

Please refer to the IB for full details.

2.5.1 Primary Pharmacology of APR-246

APR-246 has demonstrated efficacy in various preclinical *in vitro*, *ex vivo*, and *in vivo* cancer models, as single substance as well as in combination with several conventional chemotherapeutics. In many of these models APR-246 has shown good potency and efficacy and unique pharmacological profile in comparison with conventional chemotherapeutic drugs.

APR-246 reduced cell viability in a dose-dependent manner being more potent in SaOS-2-His273 cells, expressing mutant p53 than in TP53 null cells (lacking p53 expression). It also reduced cell viability in a large number of other cancer cell lines with different TP53 status. In *ex vivo* experiments with primary cancer cells from patients with AML and ovarian cancer, APR-246 reduced cell viability and, in contrast to conventional drugs, was effective also in TP53 mutant cancer cells.

A large number of solid cancer cell lines with various cisplatin sensitivity and TP53 status, were investigated in combination studies with APR-246 and cisplatin. In the various resistant cell lines tested, platinum compounds and doxorubicin showed resistance, while the sensitivity for APR-246 was considerably less affected. Strong synergistic (CI<0.5) effects with APR-246 were observed in all cell lines with homozygous hotspot TP53 mutations. These cell lines showed high levels of mutant p53 protein. Synergistic (CI<0.8) or strong synergistic (CI<0.5) effects were observed in cancer cell lines with frequently occurring TP53 mutations accumulating moderate levels of mutant p53. Variable rather than strong synergistic combination effects were observed in the cell lines with wild-type p53 and in those in which full length p53 protein is not detectable.

These results are consistent with the proposed dual mechanisms of action of APR-246, and show that APR-246 can exert its anticancer effects both in cells carrying wild type p53 and cells carrying mutant p53. Hence, both p53 dependent and independent apoptotic effects contribute to its efficacy.

Strong synergistic effects were also observed with APR-246 and cisplatin in the cisplatin-resistant ovarian carcinoma cell line OVCAR-3, carrying the TP53 hotspot mutation R248Q. APR-246 resensitized the OVCAR-3 cancer cells to cisplatin as well as to the anthracycline doxorubicin; the IC_{50} value of cisplatin was decreased 5-fold.

Strong synergistic effects of APR-246 the DNA-damaging compound doxorubicin was also seen in the doxorubicin-resistant A2780ADR ovarian cancer cell line.

2.5.2 Safety Pharmacology of APR-246

REDACTED

2.5.3 Pharmacokinetics

REDACTED

2.5.4 Toxicology

REDACTED

2.6 Previous Clinical Studies

The first clinical trial (APR-246-01) was conducted with APR-246 in patients with refractory hematological malignancies and prostate cancer. For further information please refer to the IB.

2.7 Rationale for Study in Platinum-Resistant HGSOC Population

HGSOC accounts for approximately 70% of epithelial ovarian carcinoma (EOC) in Europe and North America [10].

There are a number of active treatment options available for women with platinum-resistant EOC, including weekly paclitaxel, PLD [14] and topotecan, but the ideal treatment is not known (European Society for Medical Oncology [ESMO] EOC guidelines [15]). A Cochrane systematic review of trials (n = 1323) with platinum-resistant EOC concluded that topotecan, paclitaxel and PLD have similar efficacy, but different patterns of side effects [16]. The SmPC dose for PLD in breast and ovarian cancer is 50 mg/m^2 administered once every 4 weeks. A dose of 40 mg/m^2/4

weeks will be used in this study, as this is the dose that is almost ubiquitously used in clinical practice and is the dose recommended by an international panel of experts [17].

APR-246 may offer an opportunity to improve current treatment of platinum-resistant HGSOC patients. The rationale for this derives from preclinical evidence that MQ (i.e., the active moiety of APR-246) induces apoptosis and cell death in cancer cells with mutant TP53 or otherwise non-functional p53.

2.7.1 Preliminary APR-407 Results and Rationale for Selected APR-246 Dose and Infusion Time

REDACTED

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2.8 Characteristics of a Well-Conducted Trial

The following characteristics of an adequate and well-conducted trial will be implemented:

1. The Investigators will be well qualified by scientific training and experience.
2. Detailed electronic case report forms (eCRFs) will be completed for every patient.
3. Requirements for institutional ethics review as set forth by the appropriate Independent Ethics Committee (IEC), Title 21 Code of Federal Regulations (CFR) Part 56, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union Good Clinical Practice (GCP) Directive 2005/28/EC, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, Sections 3 and 4, and the terms of the Declaration of Helsinki (2013), will be followed.
4. Requirements for informed consent in accordance with institutional guidelines, US Food and Drug Administration (FDA) requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013), will be followed.
5. Safety data will be recorded and evaluated.
6. Routine monitoring visits will be conducted by the Sponsor's representative (Theradex®) to ensure data accuracy.
7. APR-246 accountability will be strictly maintained.
8. This trial will be conducted according to Good Clinical Practice (GCP), the protocol and applicable regulatory requirements.

3.0 TRIAL OBJECTIVES AND ENDPOINTS

3.1 Main Objectives and Endpoints

3.1.1 Primary Objective

- To assess the preliminary efficacy of APR-246 with PLD chemotherapy in patients with platinum-resistant HGSOC with mutated TP53

3.1.2 Secondary Objectives

- To evaluate the pharmacokinetics (PK) of APR-246 when administered with PLD chemotherapy
- To evaluate cardiac safety of APR-246 when administered with PLD chemotherapy
- To assess the safety and tolerability of APR-246 with PLD chemotherapy in patients with platinum-resistant HGSOC with mutated TP53
- To assess:
    - Duration of response (complete or partial response)
    - Progression-free survival (PFS) by assessment of cancer antigen 125 (CA-125)
    - PFS by RECIST 1.1
- To evaluate potential biomarkers and tumor activity based on CA-125
- To assess the biological activity in tumor and surrogate tissues.

3.1.3 Primary Endpoints

- Overall response rate according to RECIST 1.1

3.1.4 Secondary Endpoints

Secondary endpoints include the following:

- PFS rate, defined as the time from registration to the time of disease progression or relapse (according to RECIST 1.1 only) or death, or the date of last tumor assessment without any such event (censored observation)
- PK profile APR-246 and concentration in plasma

- Cardiac profile of APR-246 and concentration of PLD
- The safety profile (adverse events [AEs], laboratory assessments, physical findings and biomarkers) of APR 246 and PLD chemotherapy
- Duration of response (complete or partial response)
- Progression-free survival (PFS) by assessment of CA-125
- Evaluation of potential biomarkers
- Biological activity in tumor and surrogate tissues.

3.2 Sub-Study Objectives and Endpoints

Sub-study Objectives: Same as Main Study Objectives, except safety and tolerability, in addition to preliminary efficacy, are Primary Objectives.

Sub-study Primary Endpoint for safety and tolerability: The safety profile (adverse events [AEs], laboratory assessments, physical findings and biomarkers) of APR 246 with a shorter infusion and PLD chemotherapy.

4.0 STUDY DESIGN

4.1 Overview of Study Design

This study is an open-label, multicenter phase II study to assess whether patients with platinum-resistant TP53-mutated HGSOC will benefit from treatment with APR-246 and PLD chemotherapy. At least 25 evaluable patients will be included in this study. Patients may continue to receive treatment for as long as they are benefiting from it.

Different APR-246 infusion times will be explored. The Main Study will assess the standard 6 hour APR-246 infusion whilst the Sub-Study will explore shorter infusions (3 or 4 hour).

All patients will have pre-screening IHC to determine p53 status and therefore eligibility. Archived sections from the original tumor sample will be reviewed by a gynecological pathologist to confirm the diagnosis of HGSOC and positive IHC staining for p53. Patients without positive p53 staining will not be included.

Patients will receive standard 6 hour APR-246 infusion (fixed dose of 4.5 g APR-246) and PLD chemotherapy. After evaluation of the first six patients with the standard 6 hour infusion, a subgroup of up to 25 additional patients will be given the APR-246 dose over a shorter infusion time in order to evaluate this dosing schedule according to the same criteria as in the main study. The sub-study will be conducted in parallel with the main study.

At follow-up visits after the end of treatment, radiological tumor assessments should be performed every 8 weeks until protocol-defined progression occurs. For patients with stable disease, follow-up will take place until disease progression or until death.

All scans for each individual patient should have the same modality (CT or MRI) but CT is preferred.

A safety review committee (SRC) will evaluate the first 6 patients who receive the standard 6 hour infusion and the first 6 patients in the sub-study, to determine whether further patients can be enrolled and receive the same APR-246 infusion duration, at the same dose.

4.2 Registration of Patients

Upon completion of all screening evaluations, the center will register the patient using the Interactive Web Response System (IWRS). After successful completion of patient registration, a registration number will be issued.

Once the patient is registered through the IWRS, the patient is considered enrolled in the study. Specific instructions for the central enrollment and registration procedures are provided to the center in the study manual.

Registered patients will be assigned a unique patient identifier number. If a patient is withdrawn and replaced (as described in Section 5.3), the patient identifier number will not be reused.

4.3 Shipment of p53 samples

All archived pathology samples will be sent for centralized p53 analysis after registration and following local analysis. Labeling and shipment procedures will be provided in a separate laboratory manual.

4.4 Drug Products

4.4.1 Investigational Medicinal Product, APR-246

The study substance APR-246 (2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo [2,2,2] octan-3-one) is isolated as a white powder. APR-246 is prepared from quinuclidin-3-one in one reaction step using formaldehyde in methanol and in the presence of potassium carbonate (see IB). The IMP, APR-246 concentrate for solution for infusion, will be manufactured by Cobra BioPharma, Matfors, Sweden.

4.4.2 Reference Product PLD

PLD will be supplied by the hospital's pharmacy and will be administered in 28-day cycles.

4.5 Duration of Therapy

Patients will receive 28-day cycles of PLD chemotherapy with APR-246. Patients may continue to receive APR-246 with PLD for as long as in the Investigator's opinion they are benefiting from treatment and in the absence of disease progression and unacceptable toxicity. After the tenth 28-day cycle, data from assessments conducted within each treatment cycle will no longer be collected, but patients may continue to receive treatment after confirmation from the sponsor.

4.6 End of Study

The end of the study is defined as the date of the last visit of the last patient taking part in the study.

4.7 Study Discontinuation by the Sponsor

For reasonable cause, either the Investigator or the Sponsor may terminate this study prematurely. Written notification of the termination is required. Conditions that warrant termination by the Sponsor include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements (non-compliance).

- Lack of evaluable and/or complete data.
- Decision to modify the developmental plan of the drug.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

4.8 Treatment Plan for Patients after the Study

It is expected that patients will go on to receive treatment according to usual hospital practice.

5.0 SELECTION AND WITHDRAWAL OF PATIENTS

5.1 Inclusion Criteria

To be eligible to participate in this study, patients must meet all of the following inclusion criteria:

1. Archived sections from the original formalin fixed paraffin embedded sample reviewed by a gynecological pathologist confirming HGSOC, high grade serous peritoneal cancer or primary fallopian tube cancer and positive immunohistochemistry staining for p53 assessed according to the local methodology (as detailed in the laboratory manual). Cases that do not show p53 staining will not be included.
2. Disease progression between 4 weeks and 6 months after the last platinum-based treatment was administered.
3. At least a single (RECIST 1.1) measurable lesion.
4. Adequate organ function prior to registration:
   a) Bone marrow reserve
      - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
      - Platelets $\geq 100 \times 10^9$/L
      - Hemoglobin ≥ 9 g/dL
   b) Hepatic
      - Total bilirubin level < 1.5 x upper limit of normal (ULN) without hepatic metastasis, and < 4 x ULN with hepatic metastasis
      - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x ULN without hepatic metastasis, and < 4 x ULN with hepatic metastasis
   c) Renal
      - Calculated creatinine clearance > 30 mL/min calculated per local practice
   d) Electrolytes
      - Potassium within institutional normal ranges.
5. Toxicities from previous cancer therapies (excluding alopecia) must have recovered to grade 1 (defined by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.0). Chronic stable grade 2 peripheral neuropathy secondary to neurotoxicity from prior therapies may be considered on a case by case basis by the Principal Investigator.
6. If of childbearing potential, negative pretreatment serum pregnancy test.
7. If of childbearing potential, willing to use an effective form of contraception (see below)

during chemotherapy treatment and for at least 6 months thereafter. Such methods include the following (if using hormonal contraception, this method must be supplemented with a barrier method, preferably male condom):

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Appendix I).
9. ≥ 18 years of age.
10. Signed informed consent.

5.2 Exclusion Criteria

1. Prior exposure to cumulative doses of doxorubicin >400 mg/m^2 or epirubicin >720 mg/m^2.
2. Confirmed cardiac history of any of the following:
   a) A myocardial infarct within 6 months prior to registration,
   b) New York Heart Association Class II or worse heart failure (Appendix II)
   c) A history of familial long QT syndrome
   d) Clinically significant pericardial disease

e) Electrocardiographic evidence of acute ischemia

f) Symptomatic atrial or ventricular arrhythmias not controlled by medications

g) QTc ≥ 480 msec calculated from a single electrocardiogram (ECG) reading or a mean of three ECG readings using Fridericia's correction (QTcF = QT/RR0.33)

h) Bradycardia (< 40 bpm)

i) Left ventricular ejection fraction (LVEF) < the institution lower limit of normal as assessed by echocardiogram (ECHO).

3. Major abdominal surgery or peritonitis within 6 weeks prior to study treatment.
4. Unresolved bowel obstruction, subocclusive disease or the presence of brain metastases.
5. Hypersensitivity to PLD or to any of the excipients.
6. Unable to undergo imaging by either computed tomography (CT) scan or magnetic resonance imaging (MRI).
7. Evidence of any other medical conditions (such as psychiatric illness, infectious diseases, neurological conditions, physical examination or laboratory findings) that may interfere with the planned treatment, affect patient compliance or place the patient at high risk from treatment related complications.
8. Breast feeding.
9. Concurrent malignancy requiring therapy (excluding non-invasive carcinoma or carcinoma in situ).
10. Known HIV positive status, active hepatitis B or C status.
11. Is taking any concurrent (or within 4 weeks prior to registration) anti-cancer therapy, immunotherapy, radiotherapy, ancillary anti-cancer therapy, or any therapy that is considered to be investigational (i.e., used for non-approved indications(s) and in the context of a research investigation). Supportive care measures are allowed. Palliative limited radiation therapy for pain reduction is allowed.

5.3 Withdrawal of Patients and Study Termination

In accordance with the Declaration of Helsinki, each patient is free to withdraw from the study at any time without penalty or loss of benefits or other adequate treatments to which he/she is otherwise entitled.

Investigators also have the right to withdraw patients from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the patient, or in the case of lack of co-operation. After withdrawal of a patient, the investigator is responsible for ensuring adequate treatment and follow-up, although every effort should be made to complete all assessments at an end-of-treatment visit as listed in Section 7.2.5.

Should a patient decide to withdraw after administration of the IMP, or should the investigators decide to withdraw the patient, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given of why the patient is withdrawing or being withdrawn from the study.

The reason, time and date for withdrawal must be noted in the eCRF. If the reason for withdrawal is a clinical AE, monitoring will continue until the outcome is evident. The specific event must be recorded in the eCRF.

Patients who are withdrawn before completion of the first cycle of APR-246 and PLD as prescribed will be replaced.

The study treatment with APR-246 will be discontinued if any of the following situations occur (in the case of study termination by the Sponsor, patients will be allowed to continue to receive the standard of care):

1. Progressive disease per RECIST 1.1 criteria.
2. The development of toxicity which precludes further study treatment.
3. Patient refusal.
4. Lost to follow-up/noncompliance.
5. Significant illness that can affect the patient's ability to comply with study procedures.
6. At the discretion of the Investigator.
7. Pregnancy.
8. Study termination by Sponsor.

5.4 Compliance with Study Procedures

Patients will receive the study treatment as outlined in Section 6.0. The details of the study treatment will be documented in the eCRF and IMP accountability forms as applicable.

All study treatment related procedures will be performed in the hospital or clinic by qualified health care personnel. All instances of noncompliance and all resulting protocol deviations will be recorded by the monitors during the routine monitoring visits in the Monitoring Report.

6.0 TREATMENT OF PATIENTS

6.1 Drug Supply and Handling Procedures

6.1.1 Investigational Medicinal Product, APR-246

The IMP will be manufactured according to Good Manufacturing Practice (GMP), and labeled according to GCP, GMP and the national requirements for each site. The labels will comply with the legal requirements of the country. They will include storage conditions for the drug but no information about the study.

The IMP will be distributed in vials to the pharmacies of each participating study center. The APR-246 substance will be diluted in 0.9% sodium chloride solution at the appropriate concentration for infusion for each patient.

At the pharmacies, the IMP vials are to be stored at 2-8ºC. At the pharmacies and at the study centers, the prepared APR-246 study product (diluted in sodium chloride solution) is to be stored at not more than 25ºC. The infusion should be completed within 24 hours from the time of preparation (see Study Manual).

Detailed instructions on vial concentration, preparation and dispensing can be found in the pharmacy file.

6.1.2 Pegylated Liposomal Doxorubicin Hydrochloride

PLD will be provided from the pharmacy stock. The PLD bag used for administration will be labeled according to the local routines and regulatory requirements. The hospital will be responsible for ordering PLD. The manufacturer and batch numbers will be documented.

Please refer to the summary of product characteristics for further information on PLD.

6.2 IMP Accountability/Disposition of Clinical Trial Supplies

IMP accountability records will be maintained for all clinical trial supplies.

IMP accountability records will be kept at the pharmacy and at the study centers. The pharmacy must maintain accurate records demonstrating date and amount of IMP received, to whom and by who administered, and accounts of any IMP accidentally or deliberately destroyed.

The investigator is responsible for keeping records to ensure that:

- Deliveries of IMPs are correctly received and recorded by a designated person.
- Study medications are handled and stored safely and properly.
- Study medications are dispensed only to study patients in accordance with the protocol.
- All unused medication and empty containers are stored until they have been checked by the

study monitor.

- It is possible to reconcile records of all used and unused stocks as confirmed by the investigator's signature.

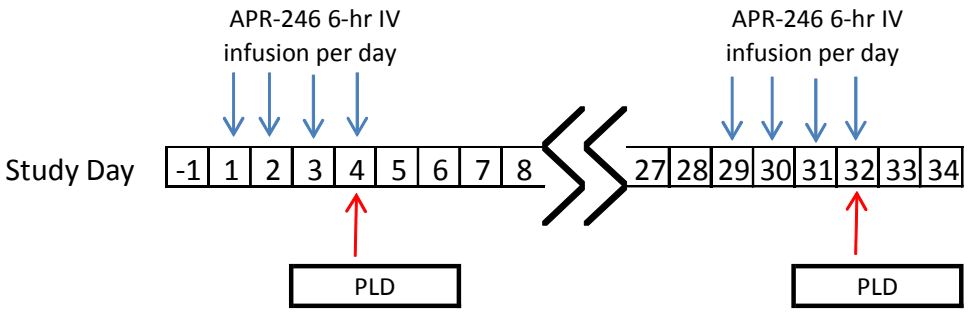
The IMP is the property of Aprea Therapeutics AB and must not be passed on to third parties. Any discrepancies between returned and expected returned IMP should be explained.

6.3 Main Study Treatment Administration

Starting within 28 days of registration, patients will receive a fixed dose of 4.5 g APR-246 (1.5 g of the dose during first 45 minutes followed by 3 g of the dose during 5 hours 15 minutes) on Days 1 to 4 with PLD 40 mg/m^2 on Day 4 (Figure 3). The PLD administration to be given on Day 4 only should commence 2 hours after the start of the APR-246 infusion.

Similarly for the following 28-day cycles, APR-246 will be administered on Days 1 to 4 with the PLD infusion on Day 4 starting 2 hours after the start of the APR-246 infusion.

Figure 3. Treatment Administration



Note: The entire dose should be given even if the infusion needs to be extended beyond a total time of 6 hours (e.g. due to slightly larger start volume in prefilled infusion bags).

APR-246 Treatment Duration

Treatment will be repeated every 28 days in the absence of disease progression or unacceptable toxicity. Supportive therapy, including growth factors, can be given as per institutional standard of care.

Pegylated Liposomal Doxorubicin Dosing

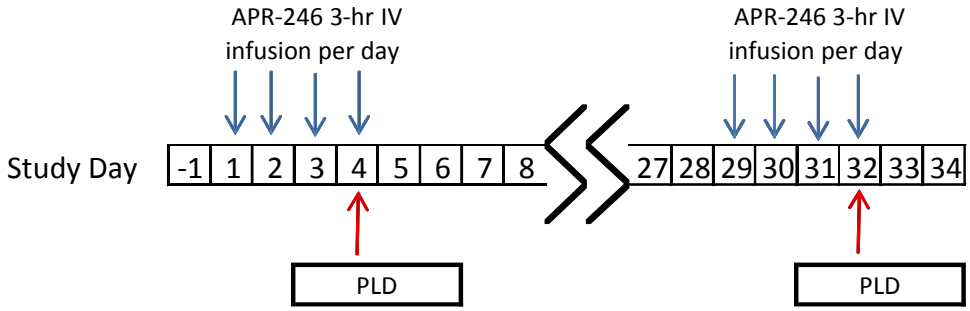
The dose of PLD will be calculated based on the body surface of the patients at 40 mg/m^2 as per standard practice at that hospital.

6.4 Sub-Study Treatment Administration

Starting within 28 days of registration, patients will receive a fixed dose of 4.5 g APR-246 in a 2-step infusion, starting with a loading dose given during first 45 minutes followed by slower infusion of the remainder of the dose, during 2 hours 15 minutes on Days 1 to 4, with PLD 40 mg/m^2 on Day 4 (Figure 4). The PLD administration to be given on Day 4 only should commence 2 hours after the start of the APR-246 infusion.

Similarly for the following 28-day cycles, APR-246 will be administered on Days 1 to 4 with the PLD infusion on Day 4 starting 2 hours after the start of the APR-246 infusion.

Figure 4. Treatment Administration in Sub-Study



Note: The entire dose should be given even if the infusion needs to be extended beyond a total time of 3 hours (e.g. due to slightly larger start volume in prefilled infusion bags).

APR-246 Treatment Duration

Treatment will be repeated every 28 days in the absence of disease progression or unacceptable toxicity. Supportive therapy, including growth factors, can be given as per institutional standard of care.

Pegylated Liposomal Doxorubicin Dosing

The dose of PLD will be calculated based on the body surface of the patients at 40 mg/m^2 as per standard practice at that hospital.

6.4.1 Sub-Study Doses and Infusion Times

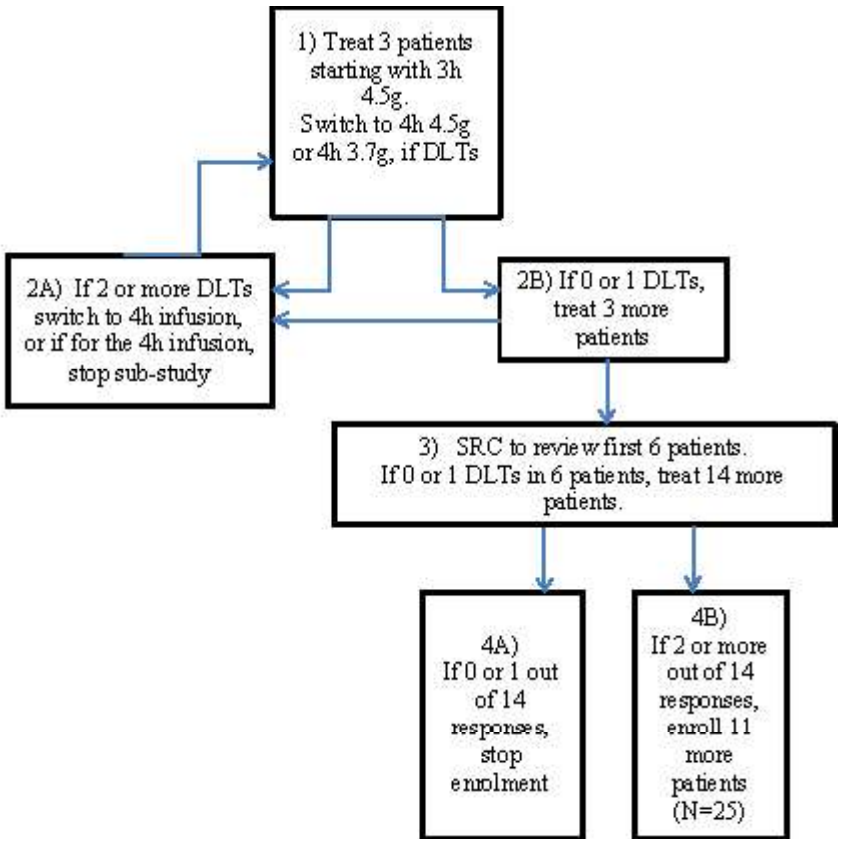
Follow the flowchart for the Sub-Study (Figure 5), starting with 3 hr 4.5 g dose. Switch to 4 hr 4.5 g infusion or 4 hr 3.7 g infusion, as indicated, based on the occurrence of dose-limiting toxicities (DLTs).

DLTs include:

- Grade 4 thrombocytopenia lasting greater than 7 days
- Grade 4 neutropenia lasting greater than 7 days
- Other grade 4 hematological toxicities which last at least 5 days
- Grade 3 or 4 febrile neutropenia
- Grade 3 or greater non-hematological toxicities; these include grade 3 or greater diarrhea, nausea or vomiting despite adequate treatment which last greater than 3 days
- Patients who are unable to be dosed for more than 5 weeks from the planned start date of the next cycle due to toxicity

Please refer to Section 6.5 for dose modification procedures.

Figure 5. Sub-Study Flowchart



6.5 Dose Modifications for APR-246 due to Adverse Events During Infusion

If a patient has any clinical adverse event ≥ grade 3 during the APR-246 infusion, the infusion should immediately be stopped. The type, severity and duration of the adverse event should be carefully assessed as well as the relationship to APR-246.

If the adverse event is considered to be unrelated to APR-246, the infusion may be resumed within 2 hours.

If the adverse event is considered to be related to APR-246, as long as all symptoms resolve to CTCAE Grade 1 or less within 2 hours, the infusion may be resumed.

In case of re-challenge, the infusion should resume at the same infusion rate (the same dose per time unit) as the initial infusion. If no symptoms occur during re-challenge, the infusion can continue until the whole dose is given and the treatment can continue according to the protocol.

If the same symptoms do occur or increase in severity during re-challenge the infusion should be stopped.

If the event lasts longer than 2 hours, then the remainder of the APR-246 infusion for that day should be discarded. If the patient has recovered sufficiently by the next day, the remainder of the planned course should be administered.

6.5.1 Main Study APR-246 Dose Reductions

After an adverse event considered as related, a single level dose reduction of APR-246 is allowed. Dose reductions are defined in Table 1. If there is a further need for a patient to have another dose reduction, this should be discussed with the Sponsor prior to any treatment decisions. The type, severity and duration of the symptoms, adverse event and infusion timings (start and stop) should be carefully documented in the patient's medical charts as per trial procedures.

Table 1. Dose Modifications of APR-246 in Main Study

Dose Modification	APR-246 Dose
Current Dose Level (DL)	APR-246 4.5 g 1.5 g (for first 45 minutes) + 3 g (for 5 hours 15minutes)
First dose reduction DL-1	APR-246 4.0 g 1.33 g (for first 45 minutes) + 2.67 (for 5 hours 15 minutes)
Second dose DL-2*	APR-246 3.5 g 1.16 g (for first 45 minutes) + 2.34 g (for 5 hours 15 minutes)

The rationale behind this dose reduction scheme is the steep relation between Cmax and dose, e.g. the suggested 11.1% and 22.2% reductions in dose results in 19.4% and 33.4% lowering of the average Cmax, respectively. See alsoAppendix III.

* Discuss with Sponsor and or medical monitor before implementing this reduction.

6.5.2 Sub-Study APR-246 Dose Reductions

After an adverse event considered as related, the infusion time may be extended to a total of 4 hours to achieve a reduced maximum blood concentration of APR-246. If a related adverse event occurs with the 4 hour infusion, APR-246 dose will be de-escalated. Dose reductions are defined in Table 2. If there is a further need for a patient to have another dose reduction, this should be discussed with the Sponsor prior to any treatment decisions. The type, severity and duration of the symptoms, adverse event and infusion timings (start and stop) should be carefully documented in the patient's medical charts as per trial procedures.

Table 2. Dose Modifications of APR-246 in Sub-Study

Dose Modification	APR-246 Dose and Regimen
Starting Regimen, 3-hour infusion	APR-246 4.5 g 2.3 g (for first 45 minutes) + 2.2 g (for 2 hours 15minutes)
4-hour infusion	APR-246 4.5 g 2.0 g (for first 45 minutes) + 2.5 (for 3 hours 15 minutes)
4-hour infusion of reduced amount*	APR-246 3.7 g 1.6 g (for first 45 minutes) + 2.1 g (for 3 hours 15 minutes)

* Discuss with Sponsor and or medical monitor before implementing this reduction.

6.5.2.1 APR-246 Infusion and Systemic PLD Chemotherapy Delays

The Day 1 to 4 APR-246 administration, together with the Day 4 PLD chemotherapy, is to be regarded as one treatment cycle and must not be administered separately.

On Day 1, prior to APR-246 administration, the hematological status of the patient should be assessed. If the patient has any hematological AE that would prevent systemic chemotherapy administration on Day 4, the APR-246 infusion and systemic chemotherapy should be delayed until recovery.

If a patient has any AE on Day 2, 3 or 4 prior to the APR-246 infusion which, in the opinion of the Investigator, would prevent systemic chemotherapy administration, the remainder of the planned APR-246 administration should be stopped. Once the patient has recovered sufficiently to receive chemotherapy, the whole treatment cycle (consisting of Days 1-4 APR-246 and Day 4 chemotherapy) should be restarted as previously planned.

If APR-246 and/or systemic chemotherapy are delayed, the reasons for delay should be recorded in the eCRF.

6.5.3 Dose Modifications for PLD

For typical hematological and non-hematological AEs seen with PLD the dose modifications should be according to the current summary of product characteristics. However, if any AEs occur that are not typical or that are considered unusual, the Sponsor should be consulted prior to re-treating the patient.

If due to AEs the patient is unable to continue chemotherapy with PLD, the patient may continue monotherapy APR-246 if the following criteria are met:

- Latest radiological scans show evidence of response.
- Patient is evaluated as not having symptoms suggestive of progressive disease.
- The Investigator assessment is that APR-246 monotherapy is of continued benefit to the patient.
- APR-246 administration has been approved by the Sponsor.

6.5.4 Cardiac Safety Monitoring in Relation to Treatment With PLD

Whenever cardiomyopathy is suspected, i.e., the LVEF has substantially decreased relative to pretreatment values and/or LVEF is lower than a prognostically relevant value (e.g., < 45%), the benefit of continued therapy must be carefully evaluated against the risk of developing irreversible cardiac damage. Cardiology consultation is recommended. Local practice should be followed.

Previous clinical trial experience with PLD for the treatment of ovarian cancer has been summarized and may be a useful reference [18].

6.5.5 Action to be Taken in the Event of QT/QTc Prolongation

Although the risk of QT/QTc prolongation is considered to be very low, in the event of prolongation of the QT/QTc interval > 500 msec or an increase of > 60 msec over baseline, study treatment should be discontinued and appropriate close (continuous) ECG monitoring in a hospital setting should be initiated until the opinion of a cardiologist is obtained.

6.5.6 Treatment of APR-246-Related Adverse Events of the CNS

If a patient reports any clinical AE of any grade during the administration period of APR-246 that could be considered to originate from the CNS (e.g., dizziness, vertigo or nausea), then the following medications may be used (Table 3). Medications of a similar nature to reflect local practice may be used.

Table 3. Examples of Rescue Medications for Use With APR-246

Indication	Supportive Measure
CNS symptoms (treatment and prevention)	Prochlorperazine 10 mg orally tid [a] Start Day -1 prior to APR-246 administration
Persistent CNS symptoms	Cyclizine 50 mg IM

[a] Prochlorperazine 10 mg orally tid (three times daily). To continue until end of Day 4 of the cycle. When used prophylactically for future treatment, start the day prior to the Day 1 administration of APR-246.

If during the infusion the patient continues to remain symptomatic intramuscular administration of cyclizine 50 mg should be considered.

6.6 Concomitant Treatment and Prohibited Medication

Patients are allowed to receive supportive care therapies (including cytokine growth factors) concomitantly during the trial.

No anti-cancer therapy other than that given in this clinical trial; no immunotherapy; no hormonal cancer therapy; no radiation therapy (except palliative); and no experimental medications are permitted during the trial. No PARP inhibitors are permitted after a beneficial response to study therapy.

Radiation therapy to index lesions should be avoided where possible; when deemed essential for patient well-being, the sponsor must be informed as the patient will become non-evaluable for endpoints assessed by RECIST, i.e. response rate and PFS.

Concomitant use of paracetamol-based compounds is allowed. However, caution should be taken when co-administrating APR-246 with high doses of paracetamol (i.e., 4 g/24 h). Use of paracetamol must be terminated if any liver function tests increase above normal ranges.

Any disease progression that requires other specific antitumor therapy will be cause for discontinuation from the trial.

Anticoagulant Therapy: Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (international normalized ratio [INR]) is monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

Concurrent or procedural medications or therapy given to or taken by the patient will be recorded in the CRF along with the indication. All concomitant medication should be recorded for up to 30 days following the last protocol treatment. After this period, only relevant medication (e.g., medication in patients with treatment-related AEs) will be recorded in the CRF.

Both generic and trade names may be recorded. However, the generic name is generally preferred because of its specificity, whereas trade names are preferred for combination products.

The potential interaction of APR-246 with other medicinal products has not been investigated.

6.7 Contraception

Female patients of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) must use a highly effective method of contraception resulting in a low failure rate (i.e., less than 1% per year) during chemotherapy treatment and for at least 6 months thereafter. These methods of contraception according to the note for guidance on non-clinical safety studies for the conduct of human trials for pharmaceuticals (CPMP/ICH/286/95, modification) include consistent and correct use of hormone containing implants and injectables, combined oral contraceptives, hormone containing IUDs, true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject and partner with vasectomy. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

7.0 STUDY PROCEDURES

7.1 Schedule of Study Procedures

Study evaluations are summarized in Table 4 below and described in Sections 7.2 through 7.2.7.

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

Table 4. Schedule of Study Evaluations

	Pretreatment[1]	Cycle 1						Cycle 2 and Subsequent Cycles					EoT	FU[12]
Day		1	2	3	4	5	19	1	2	3	4	25-28		
Eligibility Criteria	X													
Registration / Informed Consent	X													
Medical History	X	X*												
Tumor Assessment	X											X[6]	X	X
Physical Exam / ECOG	X	X						X					X	
Vital Signs	X	X	X	X	X		X**	X	X	X	X			
Hematology	X	X*			X**		X**	X*						
Coagulation	X	X*						X*						
Blood Chemistry	X	X*			X**			X*						
Creatinine Clearance	X													
CA-125	X	X*						X*					X	X
Urinalysis	X	X*						X*						
Serum Pregnancy Test (Females of Childbearing Potential)	X													
LVEF[2]	X							X[2]						
ECG in selected patients, at sites given Mortara 12-lead recorder	X	X			X[3,4]		X**[4]	X*[4]					X	
ECG in selected patients, at sites given Holter[4]	12-lead	24h Holter			24h Holter								12-lead	
ECG, non-selected patients	X												X	
Tumor Biopsy[5]	X			X										
Exploratory Biomarkers – Whole Blood	X[7]													
Exploratory Biomarkers – Plasma		X[8]						X[8]					X	X[9]

	Pretreatment[1]	Cycle 1						Cycle 2 and Subsequent Cycles					EoT	FU[12]
Day		1	2	3	4	5	19	1	2	3	4	25-28		
Administer APR-246		X	X	X	X			X	X	X	X			
Administer PLD					X						X			
Pharmacokinetics[10]		X	X[4]		X	X[4]		X			X			
New anticancer treatment[11]														X
Adverse Events and Concomitant Medication[13]	X	X												

Examinations marked * need not be repeated if already performed within +/-3 days prior to Day 1.
Examinations marked ** may be performed within +/-2 days.

1. Pretreatment evaluations to be performed within 28 days prior to Day 1.
2. LVEF assessed by echocardiography. At pretreatment and within 7 days prior to the start of Cycle 3 and Cycle 6 and every 3rd cycle thereafter. In addition, evaluation of LVEF is mandatory before each additional administration of PLD that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2.
3. Optional rhythm strip performed using limb leads of 12-lead ECG machine, after the end of APR-246 infusion.
4. These assessments will be discontinued once sufficient evaluable data has been collected.
5. An optional tumor biopsy to be performed prior to Day 1 APR-246 infusion and on Cycle 1 Day 3, as per laboratory manual.
6. CT scan/MRI at the end of Cycle 2 (within 4 days prior to the start of Cycle 3), and at the end of Cycle 4 (within 4 days prior to the start of Cycle 5) and every two cycles thereafter. In patients who have discontinued therapy without progression, scans will be performed every 8 weeks until progression has occurred.
7. Blood sample taken within 72 hours of pretreatment biopsy.
8. Blood sample taken before infusion of APR-246 in Cycles 1, 2 and 6.
9. Blood samples should be taken at each follow-up visit before progression and at progression, as per laboratory manual.
10. Pharmacokinetics: please refer to Section 8.4.
11. New anticancer treatment to be collected in eCRF during follow up.
12. Follow-up visits should be performed at least every 8 weeks.
13. AEs will be collected throughout the study, from informed consent until 30 days after the last administration of study treatment.

7.2 Detailed Study Evaluations

The following sections provide details of the study evaluations to be conducted pretreatment, during study and in follow-up. Please refer to Table 4 for a complete schedule of assessments required.

7.2.1 Registration/Informed Consent Form

Prior to performing any procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to all subject candidates and written informed consent will be obtained. Subjects who choose to participate will have to consent to the biobanking program and will be asked to sign the mandatory section in the main study consent form related to biobank samples. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study-specific evaluations. Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent.

7.2.2 Pretreatment

All pretreatment evaluations are to be performed within 28 days prior to Day 1 unless otherwise noted. Please see Table 4 for treatment windows for individual evaluations.

- **Eligibility criteria**: Including archived tumor sample review for positive IHC staining for p53.
- **Registration.**
- **Medical history.** Including documentation of all previous therapies for ovarian cancer.
- **Tumor assessment**: CT scan/MRI to be performed within 4 weeks prior to Day 1.
- **Physical examination**: Height, weight, body surface area and description of external signs of cancer. To be performed by an authorized investigator or nurse.
- **ECOG performance status**.
- **Vital signs**: Heart rate, blood pressure, respiratory rate and temperature.
- **Hematology**: Hemoglobin, hematocrit, mean corpuscular volume, platelet count, white blood cell count (WBC) and WBC differentials.
- **Coagulation**: INR and activated partial thromboplastin time (APTT). If patient is receiving warfarin, assessments should be done weekly.
- **Blood chemistry**: Sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, AST, ALT, urea, total protein, albumin and lactic dehydrogenase (LDH), direct bilirubin and uric acid.
- **Creatinine clearance**: Calculated as per hospital practice.
- **CA-125.**
- **Urinalysis**: Dipstick for protein, glucose, bilirubin and blood (perform microscopy if more than one positive dipstick test).
- **Serum pregnancy test**: For patients with reproductive potential.
- **LVEF**: Assessed by echocardiography.
- **ECG**: Standard 12-lead ECG, taken in triplicate (use Mortara ELI 150RX 12 lead ECG

Recorder if provided).

- **Tumor biopsy (optional)**: To be performed prior to Day 1 APR-246 infusion, as per laboratory manual.
- **Exploratory biomarkers**: Whole blood sample taken within 72 hours of pretreatment biopsy. The sample will be collected in order to sequence target genes of germline DNA. Archive pathology samples and blood samples to be sent for centralized analysis after registration. Refer to Laboratory Manual for detailed instructions.
- **AEs**: From the date the Informed Consent form is signed.
- **Concomitant medication**.

7.2.3 Registration

This is performed per Section 4.2. Patients should be treated within 28 days of registration.

7.2.4 All Cycles, Days 1-28

Day 1 examinations marked ***** do not need to be repeated if already performed within +/-3 days prior to Day 1. Examinations marked ****** may be performed within +/- 2 days.

- **Medical history**: Day 1*****
- **Physical examination**: Day 1. Height, weight, body surface area and description of external signs of cancer. To be performed by an authorized investigator or nurse.
- **ECOG performance status**: Day 1.
- **Vital signs**: Days 1, 2, 3 and 4. Only on Cycle 1 perform also on day 19******. Heart rate, blood pressure, respiratory rate and temperature.
- **Hematology**: Cycle 1 performed on Days 1*****, 4****** and 19****** (repeat to follow up on AEs as appropriate). Subsequent cycles perform only on Day 1*****. Hemoglobin, hematocrit, mean corpuscular volume, platelet count, WBC and WBC differentials.
- **Coagulation**: Day 1***** INR and APTT. If patient is receiving warfarin, assessments should be done weekly.
- **Blood chemistry**: Cycle 1 perform on Days 1***** and 4****** (repeat to follow up on AEs as appropriate). Subsequent cycles perform only on Day 1*****. Sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, AST, ALT, urea, total protein, albumin and LDH, direct bilirubin and uric acid.
- **CA-125**: Day 1*****.
- **Urinalysis**: Day 1*****. Dipstick for protein, glucose, bilirubin and blood (perform microscopy if more than one positive dipstick test).
- **LVEF**: Assessed by echocardiography within 7 days prior to Cycle 3 and Cycle 6 and every 3rd cycle thereafter. LVEF is mandatory before each additional administration of PLD that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2.
- **Tumor biopsy**: Cycle 1 only (optional). Tumor biopsy performed optimally at the end of APR-246 infusion on Day 3 of the first cycle, however a biopsy obtained at the end of the

APR-246 infusion on Day 2 is acceptable. Refer to Laboratory Manual for detailed instructions.

- **Exploratory biomarkers**: Blood samples taken before infusion of APR-246 on Day 1 of Cycles 1, 2 and 6. The plasma samples will be collected in order to analyze circulating tumor DNA. Refer to Laboratory Manual for detailed instructions.
- **APR-246 administration:** Days 1, 2, 3 and 4.
- **PLD chemotherapy administration:** Day 4.
- **AEs**: Even though premedicated, patients should be closely monitored for hypersensitivity reactions, especially during the first cycle.
- **Concomitant medications.**
- **Tumor assessments:** CT scan/MRI at the end of Cycle 2 (within 4 days prior to the start of Cycle 3), at the end of Cycle 4 (within 4 days prior to the start of Cycle 5) and at the end of every two cycles of treatment thereafter. In patients who have discontinued therapy without progressive disease CT/MRI scans should be performed every 8 weeks until radiological progression.
- **ECG in selected patients**: Only at centers provided with Mortara ELI 150RX 12 lead ECG Recorder. 12-lead ECG, taken in triplicate:
    - Cycle 1 Day 1
    - Cycle 1, Day 4, optional, rhythm strip performed using limb leads of the 12-lead ECG machine, after the end of APR-246 infusion
    - Cycle 1 Day 19**
    - From Cycle 2 onwards performed on Day 1* each cycle

  All recordings must be reviewed, dated and signed by the Investigator or an authorized subinvestigator. Refer to Laboratory Manual for detailed instructions.
- **12-lead continuous ECG Holter† in selected patients:** Only at centers provided with H12+ Holter Recorder. Cycle 1 only. Recorded for 24 hours, start prior to APR-246 administration on Day 1 and Day 4. Refer to Laboratory Manual for detailed instructions.
- **Pharmacokinetics**: At centers provided with H12+ Holter Recorder and Mortara ELI 150RX 12 lead ECG Recorder. Sampling for APR-246 in Cycle 1 on Day 1, 2, 4 and 5 (see Table 8); then sparse sampling for APR-246 on Day 1 and Day 4 from Cycle 2 onwards (see Table 9).†
- **Pharmacokinetics:** In all other patients: sparse sampling for APR-246 on Day 1 and Day 4 of all cycles (see Table 9).

† These assessments will be discontinued once sufficient evaluable data has been collected.

7.2.5 End of Treatment Visit

The end of treatment visit should take place 30 days (+/- 2 days) after the last APR-246 dose.

- **Tumor assessment**: CT scan/MRI. Tumor assessment should be performed at end of

treatment.

- **Physical examination**: Height, weight, body surface area and description of external signs of cancer. To be performed by an authorized investigator or nurse.
- **ECOG performance status.**
- **CA-125.**
- **ECG:** Standard 12-lead ECG, taken in triplicate (use Mortara ELI 150RX 12 lead ECG Recorder if provided).
- **Exploratory biomarkers**: Blood sample to analyze circulating tumor DNA. Refer to Laboratory Manual for detailed instructions.

7.2.6 Follow-up Visits

Follow-up visits should be performed at least every 8 weeks after the End of Treatment visit.

- **Tumor assessment**: CA-125 assessment and CT/MRI scans should be performed every 8 weeks until disease progression.
- **Exploratory biomarkers**: Blood samples taken at each visit before progression and at progression to analyze circulating tumor DNA. Refer to Laboratory Manual for detailed instructions.

7.2.7 After Progression

Survival after progression will be monitored every 6 months until death. This can be done remotely (e.g., via telephone, via general practitioner or via review of medical records).

7.3 Adverse Events

7.3.1 Definition of Adverse Events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an AE as far as the deterioration can be anticipated (see Section 7.3.4.8).

The term AE is used generally to include any AE whether serious or non-serious.

7.3.2 Definitions of Serious Adverse Events

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up) that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening (i.e., 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 was more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event (may not be immediately life-threatening or result in death or hospitalization) that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Section 7.3.4.10 below and Appendix IV.

7.3.3 SAE Exceptions

The following scenarios that may lead to hospitalization should not be considered SAEs:

- Routine treatment or monitoring of the disease under study, including hospitalization due to trial related procedures (e.g. APR-246 administration) not associated with any deterioration of the patient's status;
- Elective treatment (planned before signing Informed Consent) for a pre-existing condition that is unrelated to the disease under study and has not worsened since signing Informed Consent;
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions for an SAE;
- Social reasons, respite care in the absence of a medical condition

7.3.4 Recording of Adverse Events

7.3.4.1 Time Period for Collection of Adverse Events

AEs will be collected throughout the study, from informed consent until 30 days after the last administration of study treatment.

SAEs occurring in this period should be reported to the Theradex® Safety Desk in the usual manner (see Section 7.3.5).

7.3.4.2 Follow-up of Unresolved Adverse Events

All AEs should be followed until they are resolved or until the EOT visit, whichever comes first. All AEs that are still ongoing after the EOT visit, should be followed on a regular basis, according to the investigator's clinical judgment, until the event has resolved or until the investigator assesses it as chronic and all queries have been resolved. After the EOT visit, AEs that are unrelated to APR-246 (serious or non-serious) or related but not serious, do not require further recording in the eCRF. For Related SAEs that resolve, the date the event resolved and the outcome of Resolved or Resolved with sequelae, as appropriate, should be recorded on the eCRF and the SAE Report Form. The Sponsor retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

If an Investigator learns of any SAEs, including death, at any time following 30 days after the last administration of study treatment and he/she considers there is a reasonable possibility that the SAE is related to the study treatment, the Investigator should notify Theradex® Safety Desk.

7.3.4.3 Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date the AE started and stopped
- CTCAE version 4.0 grade
- Whether the AE is serious or not and the reason(s) it is serious
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to study treatment
- Outcome.

For SAEs, other variables will be collected including treatment given for the event.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

The grading scales found in the current National Cancer Institute CTCAE version 4.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program web site (http://ctep.cancer.gov).

7.3.4.4 Causality Collection

The Investigator will assess causal relationship between investigational product and each AE, and answer 'yes' or 'no' to the question: 'Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?'

For SAEs, causal relationship will also be assessed for other medications and study procedure(s). Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix IV.

7.3.4.5 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open-ended and non-leading verbal questioning from the study personnel (e.g., "*How are you feeling?", "Have you had any health problems since the previous visit/you were last asked?"*), or revealed by observation will be collected and recorded in the eCRF. Where possible a diagnosis should be recorded, rather than recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.3.4.6 Adverse Events Based on Examinations and Tests

The results from protocol-mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the clinical study report. Deterioration as compared to pretreatment in these parameters will therefore only be reported as AEs if they fulfill any of the criteria for a SAE, dose-limiting toxicity (DLT) or are the reason for modifying the study treatment unless clearly due to progression of disease under study (see Section 7.3.4.8).

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical events, the clinical event will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible the reporting Investigator will use the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical events, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the pretreatment assessment will be reported as an AE.

7.3.4.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and may need to be reported as SAEs if serious criteria are met. Please refer to Appendix V for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

7.3.4.8 Disease Symptomatic Management and Disease Progression

Events that are unequivocally due to the patient's underlying cancer, that occur after informed consent but before the patient is registered, should not be reported as an AE or an SAE.

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. **Events that are unequivocally due to disease progression should not be reported as AEs during the study.**

7.3.4.9 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

7.3.4.10 Handling of Deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death which is unequivocally due to disease progression should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study
- Where death is not clearly due to disease progression of the disease under study, the AE causing the death should be reported to the Theradex® Safety Desk as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes
- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death and, if performed, a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to the Theradex® Safety Desk within the usual timeframes.

7.3.5 Reporting of Serious Adverse Events

All SAEs have to be reported to the Theradex® Safety Desk, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel must inform the Theradex® Safety Desk immediately or **no later than 24 hours** of when he or she becomes aware of it.

For fatal or life-threatening AEs where important or relevant information is missing, active follow up is undertaken immediately. Investigators or other site personnel must inform the Theradex® Safety Desk of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

All SAEs require that a Serious Adverse Event Report Form be completed and forwarded either via fax or as a PDF via e-mail to the Theradex® Safety Desk at the fax number or e-mail address listed below within 24 hours of becoming aware of the event. The fax and telephone numbers listed below may be used during both business and non-business hours. During non-business hours, a recorded message will provide the caller with the contact information for the on-call monitor.

Report SAEs to:	Theradex® (Europe) Ltd. Safety Desk ***REDACTED***

SAEs will be reported according to Directive 2001/20/EC and 2005/28/EC and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

7.4 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to the Theradex® Safety Desk using the appropriate forms.

7.4.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the 30 days after

discontinuing investigational product, then Investigators or other site personnel must inform the Theradex® Safety Desk immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The same time lines apply when outcome information is available.

8.0 EFFICACY ASSESSMENTS

8.1 Definitions

Response and progression will be evaluated in this study using the international criteria (version 1.1) proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [19].

Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

8.1.1 Measurable Disease

Measurable disease is defined by the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter [LD] in the plane of measurement to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm).

8.1.2 Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam and not followed by CT or MRI.

Bone lesions, cystic lesions and lesions previously treated with local therapy must be considered as follows:

8.1.2.1 Bone Lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (i.e., CT scan or MRI) can be considered

as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

8.1.2.2 Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

8.1.2.3 Lesions With Prior Local Treatment

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

8.1.3 Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at pretreatment. Target 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). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the pretreatment sum diameter. The pretreatment sum diameters will be used as a reference by which to characterize the objective tumor response.

8.1.4 Lymph Node Assessment

For lymph nodes, measurements should be made of the short axis, which is defined as perpendicular to the LD of node assessed in the plane of measurement:
- Target lesion if short axis ≥ 15 mm
- Non-target lesion if short axis is ≥ 10 but < 15 mm
- Normal if short axis < 10 mm.

For pretreatment, add the actual short axis measurement to the sum of LD of non-nodal lesions.

8.1.5 Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at pretreatment. Measurements of these lesions are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

8.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All pretreatment evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

(Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the Sponsor/Investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.)

The same method of assessment and the same technique (CT and/or MRI) should be used to characterize each identified and reported lesion at pretreatment and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Conventional CT scan and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is acceptable in certain situations (e.g., for body scans).

Ultrasound. Ultrasound should not be used to measure tumor lesions. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date because they are operator dependent. If new lesions are identified by ultrasound, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

8.3 Response Criteria

8.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the pretreatment sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the pretreatment sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression.)
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.3.1.1 Assessment of Target Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the pretreatment exam), even if the nodes regress to below 10 mm on study. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

8.3.1.2 Target Lesions That Become "Too Small to Measure"

All lesions (nodal and non-nodal) recorded at pretreatment should have their actual measurements

recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

8.3.1.3 Lesions That Split or Coalesce on Treatment

When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter should be the maximal longest diameter for the 'coalesced lesion.'

8.3.2 Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation. (*Note:* the appearance of one or more new lesions is also considered progression.)

8.3.2.1 New Lesions

The finding of a new lesion should be unequivocal (i.e., not attributed to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor, such as a 'new' healing bone lesion). A lesion identified on a follow-up assessment in an anatomical location that was not scanned at pretreatment is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm this is definitely a new lesion, then progression should be declared using the date of the initial scan.

8.3.2.2 Evaluation of Best Overall Response by RECIST

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements

recorded since the treatment started). The patient's best overall response assignment will depend on findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 5 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at pretreatment. When patients have non-measurable disease, Table 6 should be used.

Table 5. 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, NE=not evaluable			

Table 6. 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*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response; PD=progressive disease; NE=not evaluable * Non-CR/non-PD is preferred over SD for non-target disease		

Best response determination for studies where confirmation of CR or PR is required: Complete or partial responses may be claimed only if the criteria for each are confirmed by a repeat assessment at least 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 7.

Table 7. Best Overall Response When Confirmation of CR and PR is Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR*
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; NE=not evaluable

* If CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to pretreatment, 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 the fact 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.

8.3.3 Confirmatory Measurement/Duration of Response

8.3.3.1 Confirmation According to RECIST

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6-8 weeks.

8.3.3.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (as defined by the RECIST 1.1 criteria; taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.3.3.3 Overall Response Rate

Best overall response, being confirmed and maintained for at least 28 days as defined in Section 8.3.2.2 and Table 7, will constitute the primary endpoint for response assessment and analysis.

8.3.3.4 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.3.4 Progression-free Survival

PFS is defined as the time from randomization to the time of disease progression or relapse (according to RECIST 1.1) or death, or to the date of last tumor assessment without any such event (censored observation) and includes any of the following:

- Occurrence (clinically or imaging signs) of any new lesion
- Increase in measurable and/or non-measurable tumor as defined by the RECIST 1.1 criteria

8.4 Pharmacokinetics

Please refer to the laboratory manual for detail instructions on processing of the pharmacokinetic samples.

8.4.1 APR-246

A full PK profile will be taken during Cycle 1 from patients selected for ECG Holter testing (Table 8), followed by sparse PK sampling from Cycle 2 onwards (Table 9).

For all other patients, sparse PK sampling will be done from Cycle 1 until the last Cycle (Table 9).

The objective of the sparse PK sampling scheme is to enable construction of individual PK parameters (AUC and C_{max}) for correlation with efficacy and safety. The PK of APR-246 follow a bi-exponential decline and therefore a minimum of three samples are needed to construct the PK individual profiles.

The PK sampling scheme allows for some flexibility in the timing of the blood sampling and whenever possible time windows for sample collection are given. Nevertheless it is critical for the PK evaluation that the exact times of dose administration and PK sample collection are recorded on each occasion.

Table 8. PK Blood Sampling Time Points for APR-246 During Cycle 1 (Patients Selected for ECG Holter)

Day 1	Before infusion	0-2 hrs prior to APR-246 infusion
	During infusion	5-15 min prior to end of infusion
	After infusion	15 mins +/-3 min AFTER the end of infusion
		1 hr +/-5 min AFTER the end of infusion
		3 hrs +/-15 min AFTER the end of infusion
Day 2	Before infusion	0-30 min prior to APR-246 infusion
Day 4	Before infusion	0-30 min prior to APR-246 infusion
	During infusion	5-15 min prior to end of infusion
	After infusion	15 min +/-3 min AFTER the end of infusion
		1 hrs +/-5 min AFTER the end of infusion
		3 hrs +/-15 min AFTER the end of infusion
Day 5	No infusion	12-24 hrs AFTER the end of Day 4 infusion

Table 9. Sparse PK Blood Sampling Time Points for APR-246

D1 C1*-final cycle	Before infusion	0-2 hrs prior to APR-246 infusion
	At end of infusion	+/-5 min relative to the end of infusion
	After infusion	30-60 min AFTER infusion
D4 C1*-final cycle	Before infusion	0-2 hrs prior to APR-246 infusion
	At end of infusion	+/-5 min relative to the end of infusion
	After infusion	30-60 min AFTER infusion

*From Cycle 2 (C2) in patients selected for ECG Holter testing.

8.5 Pharmacodynamics

8.5.1 Tumor Biopsies

Archived tumor tissue (formalin fixed paraffin embedded [FFPE] sections) from all patients will be reviewed by a gynecological pathologist to confirm the diagnosis of HGSOC, and positive IHC staining for p53. In addition, these samples will be used to determine p53 status by IHC by a central laboratory.

Additional analysis may include biomarkers and evaluation of tumor cell DNA.

Where possible paired tumor biopsies should be collected: one prior to treatment and the other during treatment (optimally within the last 30 minutes of the APR-246 infusion on day 3 of the first cycle, however a biopsy obtained at the end of the APR-246 infusion on day 2 is acceptable).

Two tumor cores will be taken at each biopsy, one will be flash frozen and one will be formalin fixed.

The choice of the tumor lesion is at the Investigator's discretion. The reasons for failure to obtain a biopsy must be recorded in the eCRF. If the pretreatment tumor biopsy is not obtained, no further tumor biopsies will be attempted.

Any lesion that is used for biopsy purposes should be recorded a non-target lesion only.

The following assessments may be performed by Aprea Therapeutics AB or a central laboratory appointed by Aprea Therapeutics AB (please refer to Laboratory Manual).

- Immunohistochemistry for tumor cellularity and p53 protein staining and other IHC markers (i.e., *BRCA1*, endoplasmic reticulum stress markers)
- RNA/DNA extraction for microarray tumor gene expression profiling
- Proteomics – lysates for reverse phase proteomics.

Specimens may be stored for future evaluation of APR-246 in target tissue.

The quality and quantity of the biopsy will determine which analyses are to be performed. The mutational analyses will be done in batches and the results will not be reported to the trial site during the treatment period.

8.6 Exploratory Biomarker Research

Plasma, whole blood and tumor samples will be collected from all patients and stored for retrospective exploratory analyses. These analyses may include (but are not necessarily limited to):

- Predictive markers of efficacy, tolerability and clinical pharmacology
- Biomarkers of acquired or innate resistance to APR-246

- Circulating free tumor DNA

The results of the exploratory biomarker research will be reported separately and will not be part of the Clinical Study Report.

Blood samples will be taken pre-treatment for collection of germ line DNA in order to allow comparison of germ-line and tumor cell DNA sequence. Refer to Laboratory Manual for detailed instructions.

The results of exploratory biomarker research may be pooled with data from other studies with APR-246 to generate hypotheses to be tested in future studies.

8.7 Biological Sample Handling

Details of sample collection, processing, shipping and storage will be described in the laboratory manual. Each sample for exploratory research will be identified with the study number and patient enrollment number. In this way exploratory biomarker and genetic data may be correlated with clinical data. Samples will be destroyed in the case of withdrawal of consent and regulatory audit enabled. Where genetic analysis will be undertaken the processes adopted for the coding and storage of samples will be more stringent in order to maintain patient confidentiality. As an added precaution, irrespective of the type of sample, the DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will be used to identify the sample and corresponding data at the Aprea Therapeutics AB's designated contract laboratory. No personal details identifying the individual will be available to any person (Aprea Therapeutics AB or contract laboratory staff) working with the DNA. The samples and data for genetic analysis in this study will be single coded. The link between the patient enrollment code and the DNA number will be maintained and stored in a secure environment, with restricted access. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analyzed.

8.8 Chain of Custody of Biological Samples

A full chain of custody is maintained for all samples throughout their lifecycle. The Principal Investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival. The Principal Investigator will also ensure that access to the samples while in storage at the study center will be limited only to those people for whom access is required. The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

Aprea Therapeutics AB keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers. Samples retained for further use will be registered in the Aprea Therapeutics AB biobank system during the entire life cycle. Samples will be stored for up to 15 years.

8.9 Withdrawal of Informed Consent for Donated Biological Samples

If a patient withdraws consent to the use of voluntarily donated biological samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, Aprea Therapeutics AB is not obliged to destroy the results of this research. As collection of the genetic blood sample is a voluntary part of the study then the patient may continue in the study.

9.0 STATISTICS

At least 25 evaluable patients will be enrolled in the Main Study. Up to 25 patients will be enrolled in the Sub-Study.

9.1 Sample Size

The aim is to determine the preliminary efficacy of APR-246 with PLD. The endpoint of interest is the ORR as defined in Section 8.3.2.2.

A two stage design is used to test the null hypothesis that the true response rate of APR-246 in combination with PLD is ≤10% versus the alternative that the true response rate is ≥30%. In the first stage, 16 patients will be assessed for response; if ≤1 response is seen in these 16 patients the study will be curtailed for futility. Otherwise the study will continue and a further 9 patients will be entered, for a total of 25 evaluable patients. If ≥5 responses are observed in these 25 patients, the null hypothesis will be rejected in favor of the alternative. This design provides 90.3% power and a 1-sided alpha of 9.5%.

Sub-Study Sample Size:
The aim is to determine the safety, tolerability and efficacy of a shorter infusion of APR-246 with PLD. The endpoint of interest is safety.

At one of the shorter infusion levels (3 hr 4.5 g, 4 hr 4.5 g, or 4 hr 3.7 g) if there are 0 or 1 out of 6 patients with DLTs across the first 6 patients, then an additional 8 patients will be treated for an initial total of N=14. If 0 or 1 out of 14 responses are seen, then recruitment will cease. If 2 or more out of 14 responses are seen, a further 11 patients will be recruited for a total of N=25. Observance of 5/25 responses will result in rejection of the null hypothesis. The design carries 89% power and a 1-sided type I error of 9.1% to test the null hypothesis that the true response rate is ≤10% vs the alternative that the true response rate is 30%.

9.2 General

A statistical analysis plan (SAP) will be prepared prior to data lock to expand and provide further details on the analysis and presentation of data described below.

Demographic data and disease-related characteristics will be summarized using descriptive statistics (count and percent, mean, median, standard deviation, minimum, maximum). All patient data, efficacy and safety, will be summarized similarly and fully listed.

9.3 Analysis Populations

The following populations will apply:

Safety Evaluable Population: All patients who received study medication (APR-246 or PLD) will be considered evaluable for safety regardless of the duration of treatment. This population will be used

to summarize all safety parameters.

Efficacy Evaluable Population: All patients with pretreatment measurable disease by RECIST 1.1 who have at least one radiographic assessment after pretreatment or discontinue study medication early due to disease progression and have a p53 mutation will be considered evaluable for efficacy. The efficacy-evaluable population will be the primary analysis population for efficacy.

9.4 Statistical Methods

All demographic data and disease-related characteristics will be summarized using descriptive statistics (count and percent, mean, median, standard deviation, minimum, maximum).

9.4.1 Efficacy Data

Overall Response Rate

Best overall response according to RECIST 1.1 will be presented along with the associated exact Clopper-Pearson 2-sided 95% and 1-sided lower 90% binomial confidence limits [20].

Progression-free Survival

PFS is defined as the time from registration to the time of disease progression or relapse (according to RECIST 1.1 only) or death. Patients who do not experience a PFS event will be censored at their last clinic visit contact for the assessment of disease progression.

PFS time will be summarized via a Kaplan-Meier curve with 95% confidence interval. Median PFS will be estimated from the Kaplan-Meier and presented long with 2-sided 95% confidence limits using the method of Brookmeyer and Crowley (1982) [21]. The PFS rate at 3, 6 and 9 months' follow-up will also be presented together with 2-sided 95% confidence limits using the method of Klein (2007) [22].

Evaluation of Biomarkers

The relationship between biomarkers and efficacy in terms of PFS and RECIST response will be explored using logistic regression methodology and accelerated failure time analysis.

9.4.2 Safety Data

Adverse Event Data

Safety data will be summarized for the safety evaluable population. These data will include AEs and laboratory parameters. AE terms will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA; version 16.0 or higher). AEs will be summarized by body system, preferred term, severity and relationship to treatment. SAEs, deaths and AEs leading to early discontinuation of study drug will be summarized. DLTs will be provided in a separate listing by dose. Laboratory parameters will be summarized by maximum NCI CTCAE severity grade and also by change from study entry to scheduled time points using descriptive statistics. Laboratory parameter listings will

include the normal ranges for each parameter. Each value will be classified as falling above, below or within the normal range.

Data summaries will include only treatment-emergent AEs (TEAEs), defined as events occurring on or after Day 1 Cycle 1 up to and including 30 days after last dose.

Pharmacokinetic versus ECG Parameters

The relationship between changes in ECG parameters and plasma concentration of APR-246 will be explored where possible using non-linear mixed effects modelling.

9.4.3 Pharmacokinetic data

APR-246 concentrations will be determined by a validated HPLC tandem mass spectrometry (LC/MS/MS) method. The sampling scheme is designed to allow evaluation by non-compartmental as well as population pharmacokinetic analysis. The decision on the method and whether or not the APR-246 pharmacokinetic evaluation and reporting will be done as standalone or pooled across several clinical studies with APR-246 will be taken at the time of analysis. PK parameters of APR-246 will include: Cl, Vss, C_{max}, AUC_{0-24}, $AUC_{0-\infty}$ and $t_{1/2}$.

Individual and mean profiles of concentrations of all analytes (APR-246) will be presented graphically. Protocol-specified blood sampling times will be used in the graphical presentation.

No formal statistical analysis beyond descriptive statistics is planned. For each PK parameter, individual and mean data and summary statistics (including number of subjects, arithmetic mean, geometric mean, SD, CV, median, Min and Max) will be presented.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

10.1 Monitoring of the Study and Regulatory Compliance

The project manager, or designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, and fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the initiation site visit the CRFs will be reviewed. Other pertinent study materials will also be reviewed with the Investigator's research staff. During the course of the study, the monitor will make regular site visits in order to review protocol compliance, examine CRFs and individual subject's medical records and assure that the study is being conducted according to pertinent regulatory requirements. All CRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

10.2 Curricula Vitae of Investigators

All Principal Investigators and subinvestigators will be required to provide a current signed and dated curriculum vitae and evidence of GCP training to Theradex®.

10.3 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative (Theradex®). Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IEC. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IEC by the Principal Investigator.

10.4 Publication Policy

This is a collaborative European Network for Translational Research in Ovarian Cancer (EUTROC) study. The first publication will include all patients. Centers recruiting 3 evaluable patients will be entitled to nominate one coauthor. The highest recruiting center would be entitled to be the first author on the first publication. However, the Chief Investigator would be the senior author. Contribution to sample collection and analysis for the translational components of the study will be assessed on a case-by-case basis. The Investigator agrees to inform the Sponsor of any other publication or presentations on the study. All manuscripts, abstracts or presentations (in outline form with copies of slides if available) will be submitted to the Sponsor and Theradex® at least 30 days prior to the submission of the data for publication in order for the Sponsor to protect proprietary information. The Sponsor will review the submitted material within a reasonable period of time and will not unreasonably withhold publication permission.

11.0 ETHICAL CONSIDERATIONS

11.1 Informed Consent

The Investigator will obtain written informed consent from each patient, or their authorized representative, participating in the study. The form must be signed, witnessed and dated prior to any study-specific procedures being performed. The informed consent form will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013). Copies of the signed document should be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's standard operating procedures.

In cases where minors or incapacitated subjects are to be included, two sets of information sheets might be needed according to national regulations (not applicable for the PiSARRO-R). In addition to the information given to the patient's parent or legal representative, the patient should be given information according to his/her capacity to understand. This information should include, where appropriate, a statement that the patient's decision not to participate or to withdraw from a trial will be respected, even if consent is given by the parent/legal representative.

In all instances, the Principal Investigator or an appropriately qualified delegate should consent the patient to the study. The patient should be given adequate time to read the information provided and consider whether she wants to participate in the study.

Only adult women who are mentally competent will be in enrolled and treated in this study.

11.2 Independent Ethics Committee/Regulatory

The study will not be initiated without approval of the appropriate IEC and compliance with all administrative requirements of the governing body of the institution as well as the national competent authority (CA) in each country. This protocol, consent procedures and any amendments must be approved by the IEC/CA in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH GCP. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IEC/CA will be kept informed by the Investigator, Theradex® or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected AEs.

11.3 Patient Privacy

In order to maintain patient confidentiality, all CRFs, study reports and communications relating to the study will identify patients by initials and assigned patient numbers; patients should not be identified by name. In accordance with local, national or federal regulations, the Investigator will allow the Sponsor or designee personnel access to all pertinent medical records in order to verify the data gathered on the CRFs and to audit the data collection process. Regulatory agencies such as the

FDA and the UK Medicine and Healthcare Products Regulatory Agency (MHRA) may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the patient as outlined in the patient consent form.

12.0 DATA HANDLING AND RECORD KEEPING

12.1 Data to be Recorded Directly in the Case Report Form

Not applicable.

12.2 Recording of Data

Data collected during the study will be recorded in the patient's eCRF by the investigational site staff. The staff will keep records of the patient's visit in the files considered as source documents for the site, e.g., hospital chart, research chart. The Investigator will be responsible for the recording of all data on the eCRF in a timely manner. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the CRF.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data.

12.3 Study Records

European laws require that the Investigator maintain all study records (excluding the subject's medical files, see below):

- for at least 15 years after completion or discontinuation of the trial
- or for at least 2 years after the granting of the last marketing authorization in the European Community (EC) and where there are no pending or contemplated marketing applications in the EC
- or for at least 2 years after the formal discontinuation of clinical development of the investigational product.

Subjects' medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

13.0 REFERENCES

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Appendix I: ECOG Performance Status

Grade	
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, e.g., 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.

Appendix II: New York Heart Association Heart Failure Classification

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitations, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256

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Appendix IV: Further Guidance on the Definition of a Serious Adverse Event and Interpreting the Causality Question

Further Guidance on the Definition of a Serious Adverse Event

Life threatening
'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization
Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention
Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious. Simply stopping the suspect IMP does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring i.v. hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

A Guide to Interpreting the Causality Question

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the IMP.

1. Time course. Exposure to suspect IMP. Has the patient actually received the suspect IMP? Did the AE occur in a reasonable temporal relationship to the administration of the suspect IMP?

2. Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect IMP (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
3. Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect IMP?
4. No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
5. Rechallenge experience. Did the AE reoccur if the suspect IMP was reintroduced after having been stopped? Rechallenge is not normally recommended or supported.
6. Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist. In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the IMP?
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix V: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Aprea Therapeutics AB's representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

2. Definitions

Potential Hy's Law (PHL)

AST or ALT ≥ 3 x ULN together with total bilirubin (TBL) ≥ 2 x ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law (HL)

AST or ALT ≥ 3 x ULN together with TBL ≥ 2 x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 x ULN
- AST ≥ 3 x ULN

- TBL ≥ 2 x ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory CRF.

4. Follow-up

4.1 Potential Hy's Law Criteria Not Met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol.

4.2 Potential Hy's Law Criteria Met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 6 of this Appendix)
- Notify the Theradex representative who will then inform Aprea Therapeutics AB

The Medical Monitor contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Medical Monitor
- Complete the relevant eCRF pages as information becomes available
- If at any time (in consultation with the Medical Monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Medical Monitor contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Medical Monitor and Aprea Therapeutics AB will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions

below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the SAE reporting processes as defined in Section 7.3.5 of this protocol.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to Theradex standard processes
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patient's condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change, notify the Theradex representative then follow the subsequent process described is Section 4.2 of this Appendix.

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Medical Monitor if there is any uncertainty.

7. Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, e.g., chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6 of this Appendix?

If No: follow the process described in Section 4.2 of this Appendix.

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met.

- If there is no significant change, no action is required
- If there is a significant change, follow the process described in Section 4.2 of this Appendix.

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Medical Monitor if there is any uncertainty.

8. References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf