Statistical Analysis Plan

for

Protocol DEK-DKK1-P204

A Phase 2 Study Evaluating the Efficacy and Safety of DKN-01 as a Monotherapy or in Combination with Paclitaxel in Patients with Recurrent Epithelial Endometrial Cancer, Epithelial Ovarian Cancer, or Carcinosarcoma

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Statistical Analysis Plan

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Protocol DEK-DKK1-P204

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1. List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BOR	Best overall response
BSA	Body surface area
CI	Confidence interval
CR	Complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DDE	Drug Dictionary Enhanced
DKK1	Dickkopf-1
DLT	Dose Limiting Toxicity
DoCB	Duration of clinical benefit
DoCR	Duration of complete response
DoR	Duration of response
EAS	Evaluable Analysis Set
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EEC	Epithelial endometrial carcinoma
EOC	Epithelial ovarian carcinoma
FAS	Full Analysis Set
HR	Heart rate
IHC	Immunohistochemistry

Abbreviation	Definition
MDSCs	Myeloid-derived suppressor cells
mg	Milligram
MMMT	Malignant mixed Mullerian tumor
Msec	Millisecond
NCI	National Cancer Institute
NE	Not evaluable
ODCR	Objective disease control rate
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PcD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per-Protocol
PR	Partial response
PT	Preferred Term
QTcF	Fridericia-corrected QT interval
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable disease
SI	Système internationale d'unités (International System of Units)
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid Stimulating Hormone

Abbreviation	Definition
TTP	Time to progression
TTTF	Time to treatment failure
ULN	Upper limit of normal
WHO	World Health Organization
VDS	Vita Data Sciences
VEGF	Vascular endothelial growth factor

2. Amendment History

Version	Description
1.0	Initial, based on Protocol version 5.0, dated 13-March-2019.
2.0	Updates and clarifications on the statistical analyses of the study.

3. Introduction

This SAP describes the methods to be used for analysis and reporting of clinical data collected throughout the study. It is intended to supplement the study protocol (version 6.0, dated, 1-July -2020), which contains details regarding the design and conduct of the study.

This plan should be read in conjunction with the study protocol and the electronic case report forms (eCRFs), version 4, 31-July-2019.

Note:
In this document, "study drug" refers to DKN-01 and "group" refers to the 6 distinct patient groups:

- DKN-01 monotherapy in recurrent EEC (Group 1)
- DKN-01+ paclitaxel in recurrent EEC (Group 2)
- DKN-01 monotherapy in recurrent EOC (Group 3)
- DKN-01+ paclitaxel in recurrent EOC (Group 4)
- DKN-01 monotherapy in recurrent carcinosarcoma (MMMT) (Group 5)
- DKN-01+ paclitaxel in recurrent carcinosarcoma (MMMT) (Group 6)

Pharmacokinetic and immunogenicity analyses will be conducted outside of this SAP by specialty vendors who are responsible for analyzing and writing the reports.

3.1. Change from Protocol

Analyses will be conducted in accordance with the latest Protocol version 6.0 and any changes in the analysis methods between the Protocol and SAP will be documented in the clinical study report (CSR).

Some of the changes that are observed from planned analyses in the protocol are summarized below:

- Efficacy endpoints for EEC, independent of therapy may be summarized as well.
- Efficacy endpoints of each therapy type and overall pooled may be summarized as well.
- The Evaluable Analysis Set (EAS) includes patients who received any amount of DKN-01 and have at least one evaluable post-baseline RECIST tumor response assessment or patients who were discontinued due to death, while the protocol definition had the additional condition of "discontinued due to toxicity".
- The Per Protocol (PP) Analysis Set excludes patients who have had major protocol deviations including eligibility criteria. A listing of protocol deviations will be presented on the safety analysis set and no analyses will be performed on the PP set.
- Analysis of progression free survival and time to progression will be performed only on the FAS.

- The analyses will be presented in the TFLs by cancer type (EEC, EOC, MMMT), therapy and dose (MMMT 300 mg and 600 mg) as opposed to the 6 groups noted in section 3. There were four patients enrolled in groups 2 and 3, that will be included on the summary of MMMT.

4. Study Details

4.1. Study Objectives

4.1.1. Primary Objectives

The primary objective in each independent study group (Groups 1-4) of this study is:

- To determine the objective response rate (ORR).

The primary objectives in each independent study group (Groups 5-6) are:

- To characterize the safety of DKN-01 600 mg ± paclitaxel in patients with recurrent carcinosarcoma (Malignant mixed Mullerian tumor - MMMT).
- To identify the recommended Phase 2 dose (RP2D) of DKN 01 ± paclitaxel in patients with recurrent carcinosarcoma (MMMT) based on safety, PK, and pharmacodynamics (PcD).

4.1.2. Secondary Objectives

The secondary objectives in each independent study group (Groups 1-4) of this study are:

- To determine the objective disease control rate (ODCR).
- To determine the overall survival (OS).
- To determine progression-free survival (PFS).
- To evaluate additional measures of efficacy, including time to progression (TTP), duration of response (DoR), duration of complete response (DoCR), duration of clinical benefit (DoCB), and time to treatment failure (TTTF).
- To evaluate the safety of the study treatment regimen.
- To characterize the PK of DKN-01 as monotherapy and in combination with paclitaxel in patients with recurrent Epithelial endometrial carcinoma (EEC) or Epithelial ovarian cancer (EOC).
- To detect anti-DKN-01 antibodies in human serum.

The secondary objectives in each independent study group (Groups 5-6) of this study are:

- To determine the ORR.
- To determine the ODCR.
- To determine OS.
- To determine PFS.

- To evaluate additional measures of efficacy, including TTP, DoR, DoCR, DoCB, and TTTF.
- To characterize the PK of DKN-01 as monotherapy and in combination with paclitaxel in patients with recurrent carcinosarcoma (MMMT).
- To detect anti-DKN-01 antibodies in human serum.

4.1.3. Exploratory Objectives

The exploratory objectives of this study in each independent study group (Groups 1-6) are:

- To evaluate response to therapy in patients with and without activating β-catenin mutations and/or Wnt signaling genetic alterations.
- To evaluate DKK1 concentration in serum and plasma relative to safety and efficacy outcomes.
- To evaluate tumor genetics, gene expression levels (e.g., RNA-Seq), DKK1 expression (e.g., RNAscope in situ hybridization), immunohistology, infiltrating immune cells and additional immunohistochemistry (IHC) staining (DKK1 and associated downstream elements [e.g., β-catenin]) on tumor tissue relative to safety and efficacy outcomes.
- To evaluate the frequency of myeloid derived suppressor cells (MDSCs) and T effector memory cells in peripheral blood mononuclear cells relative to safety and efficacy outcomes.

5. Randomization, Interim Analyses, and Final Analyses

5.1. Randomization

There is no randomization in this open-label Phase 2 study.

5.2. Interim Analyses

Interim analysis information will be described in the CSR.

6. Hypothesis and Decision rules

6.1. Statistical Hypotheses

Formal statistical hypothesis testing will not be performed. No multiplicity adjustments will be carried out given the descriptive nature of this trial. Unless noted otherwise, 95% confidence intervals will be presented.

7. Analysis Sets

Patients not enrolled to the study (i.e., screen failure patients) will not be included in any analysis.

The Full Analysis Set (FAS) and the Safety Analysis Set were found to be identical in terms of the number patients, since none of the patients have received paclitaxel without receiving DKN-01, therefore planned analyses have been consolidated where the intention was to repeat for both FAS and Safety Analysis Set.

7.1. Evaluable Analysis Set (EAS)

All patients who received any amount of DKN-01 and have at least one evaluable post-baseline RECIST tumor response assessment or were discontinued due to death.

7.2. Full Analysis Set (FAS)

All enrolled patients who receive any amount of DKN-01.

7.3. Safety Analysis Set

Safety population, defined as all enrolled patients who receive any amount of study treatment (either DKN-01 or paclitaxel).

7.4. Per-Protocol Analysis Set

Please refer to Section 3.1.

7.5. PK Analysis Set

PK Analysis set is evaluated outside of this SAP.

8. Endpoints and covariates

The final primary and secondary analyses of endpoints dependent on disease assessments will be performed based on investigator's assessments of disease response and progression using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

8.1. Primary Efficacy Endpoint (Groups 1-4)

Objective Response Rate (ORR) is defined as the proportion of patients with an objective response (Best Overall Response (BOR) of partial response (PR) or complete response (CR) according to RECIST 1.1).

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging in the next visit when the response was first observed with no evidence of progression between the initial and next visit.

In the case where a patient has 2 consecutive visit responses of PR, as long as there is no PD between PR visits then the patient will be defined as a confirmed PR.

Similarly, if a patient has 2 consecutive visit responses of CR, as long as there is no PD between CR visit then the patient will be defined as a confirmed CR.

8.2. Secondary Efficacy Endpoints (Groups 1-4 and Groups 5-6)

Secondary efficacy variables in the study include:

- **ORR** (i.e., BOR of CR + PR), as assessed by the Investigator using RECIST 1.1 for Groups 5-6.

- **Objective Disease Control Rate (ODCR)**

ODCR is defined as the percentage of patients with BOR of CR, PR, or SD.

- **Overall Survival (OS)**

OS is defined as the time from first dose of study drug until date of death due to any cause. Patients without documentation of death at the time of analysis will be censored as of the date the patient was last known to be alive, or the data cut-off date, whichever is earlier.

- **Progression Free Survival (PFS)**

PFS is defined as time from first dose of study drug to first documentation of PD (per RECIST 1.1) or death due to any cause.

- **Time to progression (TTP)**

TTP is defined as time from first dose of study drug to first documentation of PD (per RECIST 1.1).

- **Duration of Response (DoR)**

DoR includes only patients that have responded with an objective disease response (PR or CR) and is defined as the time from the first tumor assessment that supports the patient's objective disease response to the time of PD or death due to any cause. Patients who do not experience PD or death at the time of analysis will be censored using the same rules as described for PFS.

- **Duration of Complete Response (DoCR)**

DoCR includes patients with a CR and is otherwise defined and analyzed similarly to DoR.

- **Duration of Clinical Benefit (DoCB)**

DoCB includes patients with a BOR of CR, PR, or SD and is defined as the time from the first tumor assessment of CR, PR, or SD to the time of PD or death due to any cause. Patients who do not experience PD or death at the time of analysis will be censored using the same rules as described for PFS.

- **Time to Treatment Failure (TTTF)**

TTTF is defined as time from first dose of study drug to discontinuation of DKN-01 for any reason including PD, toxicity, and death. Patients without documentation of death at the time of analysis will be censored as of the date the patient was last known to be alive, or the data cut-off date, whichever is earlier.

<u>Censorship for OS</u>:

- Patients last known to be alive will be censored at the time of last contact.

Censorship for PFS and time-to-event analysis (except for OS):

- Patients last known to be Progression-free, and who have a baseline and at least one disease assessment after dosing, are censored at the date of the last objective disease assessment that verified lack of disease progression.
- Patients with inadequate baseline disease assessment are censored at the first dose date.
- Patients with no disease assessment after dosing are censored at the first dose date unless death occurred prior to first planned assessment (in which case the death is an event).
- Patients starting new anti-cancer treatment prior to progression are censored at the date of last objective disease assessment documenting no progression prior to the new treatment.
- Patients with documentation of progression or death after an unacceptably long interval (i.e., 2 missed or indeterminate assessments) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression.

8.3. Safety Endpoints

Overall safety profile is characterized by adverse event (AE) terms and severity of adverse events, as assigned by the investigator. Adverse events reported in the clinical trial database will be coded using the MedDRA version 18.0 dictionary. Adverse events will be graded using NCI Common Terminology Criteria for Adverse Events v5.0 guidelines (NCI CTCAE v5.0).

Safety and tolerability of DKN-01 and DKN-01 in combination with paclitaxel will be assessed using the following:

8.3.1 Treatment Emergent Adverse Event (TEAE)

Analyses of AEs will be performed for those events that are considered treatment emergent, where a TEAE is defined as any AE with an onset or worsening of a pre-existing condition on or after the first dose of the study drug through 30 days following the last dose of study drug.

- Any AE that was seen prior to the start of treatment but increased in NCI CTCAE v5.0 grade during treatment is also considered as a TEAE.
- AEs with partial dates will be assessed using the available date information to determine if they are treatment emergent. AEs with completely missing dates will be assumed to be treatment emergent.

8.3.2 Clinical Laboratory Data

Clinical laboratory assessment for this study consist of Hematology, Chemistry, Urinalysis, Coagulation studies, Pregnancy Testing, CA125, and other clinical laboratory tests like the measurement of Vitamin D, serum DKK1, plasma DKK1 and thyroid-stimulating hormone (TSH) values. For continuous laboratory parameters, the observed values and the change from baseline will be presented. Summaries will be displayed by group (tumor and therapy type) and the clinical laboratory parameters presented in alphabetical order. In the event of multiple evaluations for the same parameter at the same visit, the last non-missing value per study date/time will be used.

Clinical laboratory values will be summarized in SI units (Système Internationale d'Unités; International System of Units). Laboratory values will be assigned a toxicity grade using CTCAE version 5.0 either derived or reported. The following parameters will be included in summarizations, with asterisks (*) indicating those that will be graded using CTCAE:

- Hematology: Hemoglobin*, hematocrit, erythrocyte count (RBC), mean cell volume (MCV), mean cell hemoglobin concentration (MVHC), platelets*, leukocytes (WBC)* and differential [absolute counts of] neutrophils* (segmented and banded), lymphocytes*, monocytes, eosinophils, and basophils.
- Chemistry: Sodium*, potassium*, total bilirubin*, direct bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase*, ALT*, AST*, blood urea nitrogen (BUN), creatinine*, creatine kinase (CK), uric acid, calcium*, glucose (random), albumin*, cholesterol, serum chloride, phosphorus*, carbon dioxide, and total protein.
- Urinalysis: Specific gravity, pH, protein, glucose, ketones, blood, urine leukocyte esterase.

Hematology and chemistry laboratory results will be graded according to the NCI CTCAE v5.0 guidelines, where calculable. For these parameters shift tables will be presented of the changes from baseline grade to worst grade on study (either derived or reported). The incidence of treatment emergent Grade 3/4 clinical laboratory abnormalities will also be presented by group and DKN-01 dose levels of 300 mg and 600 mg for the MMMT group.

All laboratory data will be provided in data listings. A subset listing will be presented for all clinically significant abnormal laboratory values.

8.3.3 ECG Results

QT interval, QT_cF interval, heart rate (HR), PR interval and QRS duration will be recorded at each assessment time indicated in the schedule of activities given in the protocol. The observed baseline values and the change from baseline, for each of these assessments will be summarized descriptively. For QT_cF the number and percentage of patients in each of the following categories 450 msec, 480 msec, and 500 msec will be examined for each visit.

8.3.4 Other Safety Parameters

Other safety parameters include concomitant medications and procedures, vital signs, and Eastern Cooperative Oncology Group Performance Status (ECOG PS). Vital signs parameters namely Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Pulse, body temperature and weight, will be summarized over time in terms of observed values, changes from baseline and shifts from baseline to worst post-baseline grade.

8.3.5 PK Parameters

Pharmacokinetic analyses will be conducted by a specialty vendor who is responsible for analyzing and writing a report, hence these analyses will be outside of the scope of this SAP.

8.3.6 Immunogenicity

Immunogenicity analyses will be conducted by a specialty vendor who is responsible for analyzing and writing a report, hence these analyses will be outside the scope of this SAP.

8.3.7 Exploratory Endpoints

Exploratory analysis will be evaluated for the following exploratory endpoints relative to safety and efficacy outcomes where sufficient data (>/=5 patients) has been generated. The analyses will be performed by tumor type, therapy type and overall pooled.

- DKK1 concentration in serum and plasma
- Tumor genetics (Wnt Genetic Groups)

Wnt Signaling Alteration Definition	Wnt Activating Mutation Definition
Genes that are associated with the Wnt signaling pathways, either directly or tangentially (based on literature, FMI classification and GEO analysis) Genes: CTNNB1, APC, AXIN 1/2, RNF43, ZNRF3, RSPO2/3, WISP3, TNKS2, TERT, SOX9, SOX2, SLIT2, PAX5, NOTCH1, MLL2, LTK, LRP1B, GSK3B, GREM1, FOXP1, FBXW7, FAM123B, CREB, CDH20, CDC73, ARID1A and APCDD1	A well-defined subgroup of the genes associated with Wnt Signaling Alterations that can result in active Wnt/β-catenin dependent signaling Genes: CTNNB1, APC, AXIN1/2, RNF43, ZNRF3, RSPO2/3

Gene	Genetic alteration
CTNNB1 (β-catenin)	Protein stabilizing alteration (missense mutation of S33, S37, T41, or S45; exon 3 missense mutation or in-frame deletion of all or part of exon 3)

Gene	Genetic alteration
APC	Loss of function alteration (truncation or deletion)
AXIN1/2	Loss of function alteration (truncation or deletion)
RNF43	Loss of function alteration (truncation or deletion)
ZNRF3	Loss of function alteration (truncation or deletion)
RSPO2	Fusion protein presence (EIF3E-RSPO2)
RSPO3	Fusion protein presence (PTPRK-RSPO3)

PI3K/AKT Signaling Definition
Genes: AKT1, AKT2, AKT3, PIK3CA, PIK3CB, PIK3R1, PIK3C2B, PIK3C2G, PTEN, PDK1

- Gene expression levels (e.g., RNA-Seq)
- DKK1 expression (e.g., RNAscope H-Score and DKK1 % Positive Tumor Cells)
- Immunohistology, infiltrating immune cells and additional IHC staining (DKK1 and associated downstream elements, [e.g., β-catenin]) on tumor tissue

8.4 Covariates

Baseline data are defined as data collected which are prior to the administration of the first dose, usually on the same day as the Study Day 1 (Cycle 1 Day 1) visit. If there is more than one value on or prior to Study Day 1, the value closest to and prior to the receipt of the first dose, whether scheduled or unscheduled, will be used as the Baseline value.

The following baseline characteristics will be described and will be presented as outlined in Section 10.1 of the SAP.

Age in years, based on the date of informed consent, by <65 years and >=65 years, race, ethnicity, height (inches), weight (lbs), Body Surface Area (BSA, m^2), childbearing potential status, ECOG performance status, baseline serum DKK1, baseline plasma DKK1, baseline Vitamin D (ng/mL), baseline NLR, baseline CA125 (u/mL), primary diagnosis including tumor histology, tumor grade and stage at diagnosis, time from primary diagnosis to enrollment, prior treatment for cancer under study including the number, duration (median, 1, 2, 3 or >/= 4) and type of prior cancer therapies (systemic therapies, radiotherapy, intraperitoneal therapy and surgery). DKN-01 RNAscope H-Score will be dichotomized using tertile or statistically derived Optimal cut for PFS analysis. Upon database lock, depending on available sample sizes in each group or therapy, other methods may be considered to dichotomize DKN-01 RNAscope H-Score.

9. General Considerations for Data Analyses and Handling of Missing Values

All outputs will be produced using SAS version 9.4 or a later version.

9.1 Baseline Definition

Baseline data are defined as data collected which are prior to the administration of the first dose, usually on the same day as the Study Day 1 (Cycle 1 Day 1) visit. If there is more than one value on or prior to Study Day 1, the value closest to and prior to the receipt of the first dose, whether scheduled or unscheduled, will be used as the Baseline value.

9.2 Change from Baseline

Change from baseline is calculated as (post-baseline result minus baseline result). Percent change from baseline is calculated as (change from baseline/baseline result × 100).

If either the baseline or the post-baseline result is missing, the change from baseline, and percentage change from baseline are set to missing.

9.3 Study Day

If the date of assessment occurs on or after the first dose date, then study day will be calculated as (date of assessment – date of first dose) + 1. If the date of assessment occurs prior to the first dose date, then study day will be calculated as (date of assessment – date of first dose). There is no study day 0.

For some statistical output duration variables will be presented by months so days will be converted to months using the formula (number of days)/30.25.

9.4 Missing Data

Unless otherwise specified, missing data will be treated as missing, i.e., no special handling will be performed.

9.5 Conventions for Missing Dates

Partial dates will be displayed as is in date9. format (ddMMMyyyy).

Adverse Event

All AE onset dates must be entered on the eCRF. AEs with completely missing dates will be assumed to be treatment emergent. In the rare case that all or part of an AE onset date is missing, but an AE resolution date is present and after the first dose date, then the AE onset date will be imputed as follows for the purpose of determining the treatment emergent flag only:

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
Missing	Missing	Missing	Set date to first dose date

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
year = year of first dose	Missing	Missing/Non-missing	Set month and day to those of first dose
year ≠ year of first dose	Missing	Missing/Non-missing	Set month and day to January 1
year = year of first dose	Non-missing	Missing	Set day to the day of first dose
year ≠ year of first dose	Non-missing	Missing	Set day to first day of onset month

If AE resolution date is present and prior to first dose date, then there is no need to impute an incomplete AE onset date, as the AE is not treatment emergent and the event should be in the medical history.

Concomitant Medications/Procedures and Medical History

- If year and month are present and day is missing, then set day to first day of month for start date and set day to last day of month for end date.
- If year and day are present and month is missing, then set month to January for start date and set month to December for end date.
- If year is present and month and day are missing, then set month and day to January 1st for start date and set month and day to December 31st for end date.
- Completely missing dates will not be imputed.
- If start date is completely missing and end date is on or after the first dose, then the medication will be classified as concomitant; if the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are completely missing will be classified as concomitant.

Incomplete Date of Initial Cancer Diagnosis

- If day is missing and month is non-missing, day will be set to 15th of the month.
- If month is missing and day is non-missing, then month will be set to July.
- If month and day are both missing, month and day will be set to July 1st.
- If complete date is missing, then impute it as the date of informed consent -1.

10.Statistical Methodology and Statistical Analyses

10.1. Analysis

This is a proof of concept study and hence, the study analysis is descriptive in nature. There will be no formal comparisons between groups performed.

- For continuous variables, the descriptive statistics summary will include n, mean, standard deviation, median, 25th and 75th quartiles, upper and minimum, and maximum, will be presented.
    - DKK1 RNAscope H-Score and DKK1 Percent Positive Tumor Cells will additionally include upper and lower tertiles.
- Frequency distributions (counts and associated percentages) will be presented for categorical variables.
    - For overall summary table, percentages are based on the number of patients in each cancer group.
    - For subgroup summary tables, the percentages are based on the number of patients within each subgroup in each cancer group and treatment type.
    - For overall pooled summary table, percentages are based on the total number of patients (across all cancer groups and treatment types).
- Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. The median with 95% CI, 25th and 75th percentiles, minimum, and maximum will be presented.
- All confidence intervals (CI) will be 95%.
- Summaries will be tabulated for each group:
    - DKN-01 monotherapy in recurrent EEC
    - DKN-01+paclitaxel in recurrent EEC
    - DKN-01 monotherapy in recurrent EOC
    - DKN-01+paclitaxel in recurrent EOC
    - DKN-01 monotherapy in recurrent carcinosarcoma (MMMT)
        - 300 mg of DKN-01
        - 600 mg of DKN-01
        - Combined
    - DKN-01+paclitaxel in recurrent carcinosarcoma (MMMT)
        - 300 mg of DKN-01
        - 600 mg of DKN-01
        - Combined
    - Overall DKN-01 monotherapy
    - Overall DKN-01+paclitaxel in combination
    - Overall EEC population
    - Overall EOC population

  - Overall MMMT population
  - Overall pooled all patients
- For each group and within each group, where applicable (if there are <5 patients in a group do not run analysis), summaries will be tabulated by the presence of:
  - Wnt signaling alterations (Wnt altered vs non-Wnt altered)
  - Wnt activating mutations (Wnt activated vs non-Wnt activated)
  - CTNNB1 stabilizing mutations (CTNNB1 vs non-CTNNB1 mutated)
  - PI3K/AKT mutations (PI3K/AKT vs non-PI3K/AKT mutated
  - PIK3CA vs Non-PIK3CA mutations
  - DKK1 RNAscope H-Score, High vs Low, either tertile or statistically derived optimal cut in PFS analysis for each group by therapy type (i.e. mono or combo therapy, overall)
- Adverse Events, laboratory data, vital signs, ECG, ECOG, concomitant medications and procedures, and exposure summaries will be tabulated as following:
  - DKN-01 monotherapy (300 mg) in recurrent EEC
  - DKN-01+paclitaxel (300 mg) in recurrent EEC
  - DKN-01 monotherapy (300 mg) in recurrent EOC
  - DKN-01+paclitaxel (300 mg) in recurrent EOC
  - DKN-01 monotherapy in recurrent carcinosarcoma (MMMT)
    - 300 mg of DKN-01
    - 600 mg of DKN-01
  - DKN-01+paclitaxel in recurrent carcinosarcoma (MMMT)
    - 300 mg of DKN-01
    - 600 mg of DKN-01
  - All Patients who received DKN-01 (300 mg)
- Overall by monotherapy and combination therapy, by tumor type and overall pooled analysis summaries will also be tabulated on:
  - Relationship between DKK1 RNAscope tumoral levels and genetics (Wnt Altered, Wnt Activated, and PI3K/AKT)
  - Relationship between DKK1 RNAscope tumoral levels and serum and plasma DKK1 levels
- Individual patient data listings, sorted by patient number, will be provided to support summary tables.
- Graphical presentation of efficacy and safety endpoints will be displayed as and when needed.

10.2. General Principles

The efficacy endpoints for each group will be analyzed as stated under Sections 10.3 and 10.4. When assessing safety and tolerability, summaries will be produced based on the Safety Analysis set. The safety data will be summarized descriptively and will not be formally analyzed.

10.3. Primary Efficacy Analysis

ORR is as per investigator's assessment according to RECIST 1.1. The proportion of patients with an objective response (BOR of PR or CR according to RECIST 1.1, unconfirmed and confirmed ORR) in the EAS, along with a 95% CI, based on Clopper-Pearson will be reported.

CR is confirmed when CR is followed by a subsequent finding of CR and PR is confirmed when PR is followed by a subsequent finding of PR/CR, in the EAS.

Best overall response will also be summarized using the EAS.

Secondary analyses of ORR described above will be repeated in the FAS, treating missing BOR as a non-responder and will be displayed as 'Missing'.

Additional subgroup and supportive analyses of ORR will be performed for overall patients. Initially, univariate logistic regression may be performed to select the perspective covariates and then multivariate logistic regression analysis will be performed on the selected covariates from univariate analyses. Wnt signaling alterations (yes/no), Wnt activating mutations (yes/no), CTNNB1 mutations (yes/no), PI3K/AKT mutations (yes/no), PIK3CA mutations (yes/no), and DKK1 RNAscope H-Score (high vs low utilizing either tertile analysis or optimal cut) will be analyzed using logistic regression model adjusting for covariates (Tumor type, age <65 vs >= 65 years, etc.) in the model.

The odds ratios (ORs) and 95% CI will be summarized and presented on a forest plot.

If the sample size permits, additional multivariate logistic regression analyses will be performed for overall by tumor type and/or by therapy type.

10.4. Secondary Efficacy Analysis

The following table details the analysis of the secondary efficacy endpoints. Additional subgroup analysis will also be performed on the secondary endpoints for overall patients: Wnt signaling alterations (yes/no), Wnt activating mutations (yes/no), CTNNB1 mutations (yes/no), PI3K/AKT mutations, (yes/no), PIK3CA (yes/no) and DKK1 RNAscope H-Score (high vs low utilizing either tertile analysis or optimal cut) will be analyzed using Cox regression model adjusting for covariates (Tumor type, age <65 vs >= 65 years, etc.) in the model. For PFS and OS, supportive multivariate Cox regression analyses will be performed.

The hazard ratios (HRs) and 95% CI will be summarized and presented on a forest plot.

If the sample size permits additional multivariate Cox regression analyses will be performed for overall by tumor type and/or by therapy type.

Efficacy Endpoint	**Analysis Set**	**Analysis**
ODCR	EAS	• Percentage of patients with BOR with CR, PR or SD • Clopper-Pearson 95% confidence interval • Both ODCR and confirmed ODCR ○ Confirmed ODCR is defined as the percentage of patients with a BOR of confirmed CR, confirmed PR, or SD • SD is confirmed when SD is followed by a subsequent finding of CR/PR/SD
OS	FAS	• Median event time (25th and 75th percentiles) • Min and Max • Corresponding 95% CI • Landmark OS (95% CI calculated based on the Kaplan-Meier method) in months • Forest plot for the hazard ratio (based on Cox regression model) and 95% CI when summarized by Biomarkers
PFS	FAS	• Median event time (25th and 75th percentiles) • Min and Max • Corresponding 95% CI • Landmark PFS (95% CI calculated based on the Kaplan-Meier method) in months • Forest plot for the hazard ratio (based on Cox regression model) and 95% CI when summarized by Biomarkers
TTP	FAS	• Median event time (25th and 75th percentiles) • Min and Max • Corresponding 95% CI
DoCR, DoR and DoCB	EAS	• Median event time (25th and 75th percentiles) • Min and Max • Corresponding 95% CI
TTTF	FAS	• Median event time (25th and 75th percentiles) • Min and Max • Corresponding 95% CI

10.5. Study Drug Exposure

Extent of Treatment:

- Number and percent of patients beginning 1, 2, 3, 4, 5, 6 and > 6 cycles and number of cycles started (mean, median, minimum, maximum) will be reported.
- Overall treatment duration (days), defined as date of last dose of study drug – date of first dose of study drug + 1. Treatment duration for each individual study treatment (e.g., DKN-01 and paclitaxel) is defined as the last dose date of the treatment – first dose date of the treatment + 1.
- Duration of post-treatment follow-up (days), defined for patients who entered the post-treatment follow-up period as date of death – date of last dose of study treatment + 1 (for patients who died), and defined as the last visit date – date of last dose of study treatment + 1 otherwise.
- Duration of study participation (in days and this includes DKN-01 mono or DKN-01 + paclitaxel combo treatment and follow up), defined as end of study date – date of first dose of study drug + 1.

Summary of Study Drug Administration:

Tables will be provided by treatment cycle and all treatment cycles, by DKN-01 and paclitaxel, for the following (receiving any dose in the cycle is counted as a treatment cycle):

- Dose planned
- Dose received
- Relative Dose (i.e. percent of actual total dose received relative to intended total dose initially planned per protocol, where actual total dose= total dose received as recorded on eCRF; intended total dose = (prescribed dose at beginning of the study)*(actual dose duration))

Dose Delays and dose modifications:

- Patients with at least one dose reduction; patients with at least one dose reduction due to an adverse event, total number of dose reductions will be tabulated
- Number of dose interruption/missed by cycle and all cycles.

10.6. Adverse Events

Only summaries of Treatment Emergent Adverse Events (TEAEs) will be provided. The following summaries will be done on the safety analysis set:

- Overall Summary of TEAEs
  - Any TEAE
  - Any TEAE related to DKN-01
  - Any TEAE related to paclitaxel
  - Any Grade 3+ TEAE
  - Any Grade 3+ TEAE related to DKN-01

  - Any Grade 3+ TEAE related to paclitaxel
  - Any TESAE
  - Any TESAE related to DKN-01
  - Any TESAE related to paclitaxel
  - Any TEAE leading to withdrawal of DKN-01
  - Any TEAE leading to withdrawal of paclitaxel
  - Any TEAE leading to dose reduction
  - Any TEAE leading to dose reduction of DKN-01
  - Any TEAE leading to dose reduction of paclitaxel
  - Any TEAE leading to dose interruption
  - Any TEAE leading to dose interruption of DKN-01
  - Any TEAE leading to dose interruption of paclitaxel
  - Any TEAE leading to dose omission
  - Any TEAE leading to dose omission of DKN-01
  - Any TEAE leading to dose omission of paclitaxel
  - Any Infusion-related TEAE
  - Any DKN-01 Infusion-related TEAE
  - Any paclitaxel Infusion-related TEAE
  - Any TEAE leading to Death
  - Any DKN-01 related TEAE leading to Death
  - Any paclitaxel related TEAE leading to Death
  - Patients with Dose Limiting Toxicity (DLT)
- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- Treatment-related TEAEs by SOC and PT
- TEAEs leading to DKN-01 discontinuation by SOC and PT
- Treatment-related TEAEs leading to DKN-01 discontinuation by SOC and PT
- TEAEs leading to DKN-01 dose reduction/interruption by SOC and PT
- TEAEs leading to paclitaxel discontinuation by SOC and PT
- Treatment-related TEAEs leading to paclitaxel discontinuation by SOC and PT
- TEAEs leading to paclitaxel dose reduction/interruption by SOC and PT
- TEAEs by SOC, PT, relationship, and grade
- Listing of deaths
- Treatment Emergent Serious Adverse Events (TESAEs) by SOC and PT
- TEAEs with CTCAE grade 3 or higher by SOC and PT
- Treatment-related TEAEs with CTCAE grade 3 or higher by SOC and PT
- TEAEs by PT
- DKN-01-related TEAEs by PT
- Infusion-related TEAEs by PT

A patient with more than one occurrence of the same adverse event in a particular system organ class and preferred term will be counted only once in the total of those experiencing adverse events in that particular system organ class and preferred term respectively. If a patient experiences the same adverse event at more than one severity, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence.

An AE will be considered to have a study drug relationship of related if the eCRF response was either possibly or definitely related.

All missing AEs Grades and relatedness will be queried for a value. If a Grade or AE relatedness cannot be obtained, the missing values will be treated as unknown.

10.7. Laboratory Data (Hematology, Chemistry, Urinalysis and Other Laboratory Tests)

For all continuous laboratory assessments, observed values, and change from baseline will be summarized using descriptive statistics at each scheduled assessment time by group.

Shift tables (baseline grade to worst post-baseline grade on study) for laboratory values by NCI CTCAE grade (Grade 0, 1, 2, 3, 4, 5, Missing and total) will be produced. For all categorical laboratory assessments, counts and percentages will be presented at each scheduled assessment time by group. Refer to section 8.3.2.

CA125, serum DKK1, plasma DKK1, TSH, and Vitamin D, will be summarized in the Other laboratory tests and a corresponding listing will be generated. Pregnancy testing information will also be listed in the Other laboratory tests listing. The shift from baseline grade to worst grade on study will also be presented for these other lab tests.

10.8. Hy's Law

A summary table and a corresponding plot will be presented by group to evaluate the Drug-Induced Serious Hepatotoxicity (eDISH). The number (n) will be the number of patients in each treatment group.

Definition of Hy's Law:

- ALT/AST elevations >= 3*ULN and
- Total Bilirubin elevations >= 2*ULN
- No alternative cause for ALT/AST/Total Bilirubin elevations

10.9. Electrocardiograms (ECG)

All ECG parameters will be summarized descriptively at each scheduled assessment by tumor type, therapy type and dose. The change from baseline will also be tabulated. The number and

percentage of patients with QTcF values in the following categories will also be presented by tumor type, therapy type and dose:

- Value at visit: >450 msec, >480 msec, >500 msec
- Change from baseline: >20 msec >30 msec, >60 msec

Baseline will be defined as the readings prior to dosing on the first day the study medication is administered.

The maximum absolute value post dose and the maximum increase from baseline over all measurements taken post dose will be determined.

The maximum increase from baseline will be calculated by subtracting the baseline value from each post dose measurement to give the change from baseline. The maximum of these values will then be selected, except in the case where a subject does not show an increase, in such an instance the minimum decrease should be taken.

10.10. Vital Signs and Weight

Vital signs parameters namely Systolic Blood Pressure, Diastolic Blood Pressure, respiratory rate, pulse, temperature, and weight, will be summarized over time in terms of observed values and changes from baseline, at each scheduled measurement by group. A shift table comparing the baseline value to maximum value on study, will be summarized for each of the vital signs by group.

10.11. Physical Examination

The physical examination data will be listed.

10.12. ECOG Performance Status

ECOG Performance Status (PS) will be summarized as a shift from the baseline score to the maximum status on study (i.e. worst ECOG score) over time by group.

10.13. Disposition, Demographic and Baseline Characteristics

The following disposition data will be summarized by group and by biomarkers (except the number and percentage of patients enrolled by site):

- Number of enrolled patients (enrolled patients includes all patients that are enrolled and treated on Cycle 1 Day 1)
- Number and percentage of patients enrolled by site (based on the enrolled patients)
- Number and percentage of patients in each of the analysis sets
- Number and percentage of patients who discontinued the study treatment, DKN-01 and paclitaxel

- Number and percentage of reasons for withdrawal from the study treatment, DKN-01 and paclitaxel
- Number and percentage of patients who discontinued the study
- Number and percentage of reasons for trial participation ended

The demographic and baseline characteristics data will be summarized by group for the parameters mentioned under Section 8.4, along with Age (<50 years, 50-59 years, 60-69 years, 70-75 years, >75 years), baseline serum DKK1, baseline plasma DKK1, baseline vitamin D, baseline NLR, and baseline CA125.

The following additional patient characteristics will be summarized and listed by group on the safety analysis set:

- Medical history:
  - General medical and surgical history by SOC and PT will be summarized, and a corresponding listing will be generated which will include the CTCAE grade
- Cancer history by:
  - primary diagnosis (e.g., EEC, EOC, MMMT), histology, stage at initial diagnosis, tumor grade at initial diagnosis, time from primary diagnosis to enrollment (days), time to recurrence/progression, any current known metastatic disease site at baseline, sites of metastatic disease
- Prior-disease related therapies:
  - Prior Systemic Therapy and intent of prior Systemic Therapy (adjuvant, locally advanced, metastatic disease, neoadjuvant, radio sensitizing)
    - Prior Systemic Therapies: Taxane, VEGF inhibitors (e.g., Avastin), Platinum therapy, platinum status (ovarian cancer only- sensitive, resistant, or refractory), PARP inhibitors, Immunotherapy (IO), hormonal therapy
  - Prior Surgery and intent of prior surgery (diagnostic, palliative, curative)
  - Prior Radiation therapy
  - Prior Intraperitoneal Therapy
- Concomitant medications will be summarized by World Health Organization (WHO) Drug Dictionary Enhanced (DDE), September 2016 version. Patients are counted only once within each ATC level 1 term and WHO Preferred Name
- Concomitant blood transfusions
- Concomitant procedures coded by MedDRA version 18.0 will be summarized.

10.14. Exploratory Analysis

The following exploratory endpoints will be summarized:

- Summary of Tumor Mutational Burden and the number and percentage by following:
  - 0 to < 6 (Low)
  - >= 6 to 20 (Intermediate)
  - >= 20 (High)
  - Missing
- Microsatellite Status (MSS, MSI-H, MSI-L, MSI ambiguous and MSI unknown)
- DKK1 expression
  - RNAscope H-Score: High and Low (either tertiles or statistically derived based on the optimal cut in PFS analysis)
  - RNAscope H-Score % Positive Tumor Cells
- Baseline MDSCs (%)
- Baseline CD4 (%), CD4+/CD45RA-CCR7-/KI67+ (%), CD8 (%), CD8+/CD45RA-CCR7-/KI67+ (%), NK (%)
- Tumor Genetics as described under Section 8.3.7

11. References

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