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STATISTICAL ANALYSIS PLAN

A Phase 2 study to assess the safety, efficacy of FLX475 combined with Pembrolizumab in patients with advanced or metastatic gastric cancer

PROTOCOL NO.: HM-CCRI-201

PRODUCT CODE: FLX475

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[redacted]

SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed by Hanmi Pharmaceutical Co., Ltd. and has been approved for use on the HM-CCRI-201 study:

Name	Title / Company	Signature	Date
[redacted]			

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List of Abbreviations

Abbreviation	Description
AE	Adverse Event
ATC	Anatomical Therapeutic Class
AUC	Area under the curve
BMI	Body mass index
BLQ	Below limit of quantification
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CR	Complete response
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient of Variation
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DBP	Diastolic blood pressure
DCR	Disease control rate
DoR	Duration of response
EBV	Epstein-Barr Virus
ECG	12-Lead Electrocardiogram
ECIs	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
iCPD	immune Confirmed Progressive Disease
iCR	Immune-based complete response
iDCR	ORR according to iRECIST
IDMC	Independent Data Monitoring Committee
iDoR	DoR according to iRECIST
iORR	ORR according to iRECIST
iPFS	PFS according to iRECIST
iPR	Immune-based partial response
iRECIST	Modified RECIST for immunotherapies
iSD	Immune-based stable disease
iTTR	TTR according to iRECIST
iUPD	Immune-based unconfirmed progressive disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
mmHg	Millimeter of Mercury
MUGA	Multiplegated Acquisition
NK	Not Known
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response

Abbreviation	Description
PT	Preferred Term
QD	Once daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
Sd	Standard deviation
SD	Stable disease
S.I.	International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
$T_{1/2}$	Terminal phase elimination half-life
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to maximum concentration
TTR	Time to response
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data collected from the **HM-CCRI-201** study (protocol version 3.0 dated 6 December 2022).

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

2. PROJECT OVERVIEW

2.1 Study Design

This clinical study is a Phase 2, open-label study to assess the efficacy, safety profile of FLX475 combined with pembrolizumab in patients with advanced or metastatic gastric cancer. Approximately 90 subjects may be enrolled across two cohorts to examine the safety and efficacy. This study is designed to assess the potential anti-tumor activity when administered at the 100mg QD of FLX475 with pembrolizumab and will be conducted (2) cohorts as detailed below.

Cohort 1: Checkpoint inhibitor naïve Epstein -Barr Virus (EBV) negative gastric cancer subjects who have progressed on at least 2 prior systemic treatments for advanced or metastatic gastric cancer

Cohort 2: Checkpoint inhibitor naïve Epstein -Barr Virus (EBV) positive gastric cancer subjects who had at least 1 prior systemic treatment for advanced or metastatic gastric cancer

Cohort 1 will be enrolled in two stages, starting with at least 10 subjects in the first stage. Expansion to the stage 2 of cohort 1 will be based on the overall safety and efficacy data as well as any available PK and PD data when the 10th subject completes 4 cycles (or 12 weeks; after 2nd response assessment) or withdrawn from the study, whichever occurs first. During this data review, Sponsor can determine study discontinuation if there is no responder from 10 subjects in the first stage. Once expanded, 20 additional subjects will be accrued in stage 2 and further assessment for the safety and efficacy based on the accumulated data up to 30 subjects (10 from stage 1 and 20 stage 2) will be performed. Referring to the published data, 15% of ORR is the minimum criteria to proceed for the next stage in the study. If the posterior probability for the ORR $\geq$ 15% is less than 80%, the enrollment to the cohort will be paused and assessed overall safety along with PK and PD data available. In consideration of the cumulative overall safety and efficacy up to the 30 subjects along with the other competitive landscape, the cohort 1 could be expanded further up to 60 subjects at maximum including the previous subjects enrolled or could be stopped for further enrollment. Also, if required, there could be another stage to investigate further after 2nd stage as well.

Cohort 2 will be enrolled in similar way to the cohort 1 starting with 10 subjects in the first stage and expanded to the second stage based on the overall safety and efficacy as well as available PK and PD data when the 10th subject completes 4 cycles (or 12 weeks; after 2nd response assessment) or withdrawn from the study, whichever occurs first. During this data review, Sponsor can determine study discontinuation if there is no responder from 10 subjects in the first stage same as cohort 1. Referring to the published data, for cohort 2 30% of ORR is the minimum criteria to proceed for the next stage in the study. Once determined to the second stage, additional 10 subjects will be enrolled for cohort 2 and if the posterior probability for the ORR $\geq$ 30% is less than 80%, the enrollment to the cohort will be paused and assess overall safety along with PK and PD data available. If required, further enrollment up to 30 in total as maximum might be performed based on the overall data up to 20 subjects in comparison with the competitive landscape. Also, if required, there could be another stage to investigate further after 2nd stage as well.

The next stage of each cohort will be determined after the comprehensive evaluation from the previous stage by the Independent Data Monitoring Committee (IDMC).

To study potential PD biomarker changes that may be indicative of combined pathway inhibition by the pembrolizumab and FLX475 combination, paired (pre- and post-treatment) tumor biopsies will be obtained from all subjects.

The screening period (Day -30 to Day -1) lasts up to approximately 30 days prior to Cycle 1 Day 1. Patients must meet all Inclusion/Exclusion Criteria to participate in the study. All screened patients will provide written Informed Consent prior to any study procedures.

Once screening procedures are completed and eligibility is confirmed, subjects will start treatment Cycle 1 with FLX475 and pembrolizumab on Day 1. Subject will continue to receive study treatment for a maximum of 35 cycles (approximately 2 years) or until subject withdrawal from the study, confirmed progression of cancer, intolerable study treatment-related toxicity despite appropriate dose modification

and supportive treatment, pregnancy or breastfeeding, substantial noncompliance with study procedures, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

For subjects who have radiological Progressive Disease (PD) by Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 as determined by the investigator will decide whether the subject can continue to receive study treatment until repeat, confirmatory imaging is obtained using modified RECIST for immunotherapies (iRECIST) for subject management.

The extension part will provide continued access to FLX475 combined with pembrolizumab to subjects who have previously participated in HM-CCRI-201 study and are ongoing from the treatment with clinical benefit.

The primary objective of the extension part mainly is to provide continued treatment with FLX475 combined with pembrolizumab without the previous study procedures that intended to collect data for further analysis (e.g. efficacy, safety, biomarker, etc.). Survival and post-therapy long-term follow-up will also be discontinued.

2.2 Objectives

To evaluate safety and anti-tumoral effect of FLX475 combined with pembrolizumab in subjects with advanced or metastatic gastric cancer. The primary and secondary efficacies will be evaluated by RECIST 1.1 and iRECIST.

2.2.1 Primary objectives

To assess the anti-tumor efficacy of FLX475 in combination with pembrolizumab in subjects with advanced or metastatic gastric cancer by Objective Response Rate (ORR) by RECIST 1.1.

2.2.2 Secondary objectives

- To assess of the clinical efficacy including DCR (complete response + partial response + stable response), TTR, DoR, and PFS by RECIST 1.1
- To assess OS
- To assess of the clinical efficacy by iRECIST including iORR, iDCR, iTTR, iDoR, iPFS
- To assess the safety and tolerability of FLX475 combined with pembrolizumab based on Laboratory assessments and AE, SAE using NCI-CTCAE v 5.0

[redacted]

2.3 Endpoints

2.3.1 Primary endpoint

- Objective Response Rate (ORR, complete response + partial response) by RECIST 1.1

2.3.2 Secondary endpoints

- Efficacy in accordance with RECIST 1.1: DCR, TTR, DOR, PFS
- Efficacy in accordance with iRECIST: iORR, iDCR, iTTR, iDOR, iPFS
- Efficacy: OS

- Safety and tolerability: AEs, Laboratory assessments (including hematology, biochemistry, coagulation, urinalysis, vital signs, physical examination, ECG and ECOG)

[redacted]

[redacted]

2.4 Sample Size

There is little known about the objective response rate from the subjects who have progressed on at least 2 prior systemic treatments for advanced or metastatic gastric cancer excluding check point inhibitor (CPI). In addition, considering the study nature to explore the safety and efficacy by FLX475 and pembrolizumab, no formal statistical testing will be done. As stated in the study design part, each cohort will enroll target subjects separately and both cohorts will initiate 2-stage design. The initial number of target subjects for the 1st stage for both cohorts is determined as 10 based on feasibility. However, the target subject number for the 2nd stage would be determined based on the overall safety assessment and the posterior probability of at least 80% to achieve the ORR ≥ 15% and ORR ≥ 30% for cohort 1 and cohort 2, respectively.

The posterior probability for ORR ≥ 15% and ORR ≥ 30% for cohort 1 and 2, respectively, based on the responses in the first and second stage is described in the Table 11.1:1 and Table 11.1:2 below assuming uniform prior distribution for ORR. For example, if we observed 1 response out of the initial 10 subjects of cohort 1 at 1st stage followed by 6 responses out of additional 20 subjects at 2nd stage, we could assume that the probability of ORR ≥ 15% by FLX475 and pembrolizumab combination therapy would be 92% based on the observed data (Table 11.1:1). Also, if we observed 1 response out of the initial 10 subjects of cohort 2 at 1st stage followed by 7 responses out of additional 10 subjects at 2nd stage, we could assume that the probability of ORR ≥ 30% by FLX475 and pembrolizumab combination therapy would be 85% based on the observed data (Table 11.1:2).

Considering the minimum posterior probability of 80% to achieve ORR ≥ 15% for cohort 1 and ≥ 30% for cohort 2 as well as the overall safety data, the total number of subjects for each cohort will be adjusted after each stage.

- Prior distribution for ORR (P) ~ Unif (0,1)
- Observed data X ~ Binomial (N, P)
- Posterior distribution for ORR, (P| X) ~ Beta (1+X, 1+N-X).

- **Table 11.1:1 Posterior probability of ORR ≥ 15% for Cohort 1 by number of subject and response**

[redacted]

[redacted]

- **Table 11.1:2 Posterior probability of ORR ≥ 30% for Cohort 2 by number of subject and response**

[redacted]

2.5 Randomization

Not applicable.

3. STATISTICAL CONSIDERATIONS

Data will be handled and processed per the sponsor's representative [redacted] Standard Operating Procedures (SOPs), which are written based on the principles of good clinical practice (GCP).

3.1 General Considerations

All data collected on the electronic case report form (eCRF) will be presented in the data listings. In general, all data will be summarized with descriptive statistics for continuous endpoints (variables), and frequency and percentage for categorical endpoints (variables) unless other specified. As each cohort will enroll target subjects separately and so the analysis will be performed separately for each cohort as well. The data summaries will be presented by stage and overall across stages for each cohort.

Summary of treatment exposure, concomitant medication, pharmacokinetics, and all safety descriptive summaries will be presented by cohort.

Unless otherwise stated, the following methods will be applied:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (Sd), median, minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data/eCRF data, the arithmetic mean and median values will be displayed to one more decimal than the source data for the specific variable. Sd will be displayed to two more decimal than the source data for the specific variable.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the above mentioned rules.

- PK data: For PK concentration data, the number of non-missing values, number of below limit of quantification (BLQ) values, arithmetic mean, standard deviation, median, minimum, maximum, coefficient of variation (CV%), geometric mean and geometric coefficient of variation (geo CV%) values will be presented. For the calculation of summary statistics, unrounded data will be used and reported to three significant figures with the exception of n, nBLQ, and CV% which will be presented to the nearest integer and one decimal place, respectively.

  For PK parameter data, the number of non-missing values, arithmetic mean, standard deviation, median, minimum, maximum, CV%, geometric mean, and geo CV% values will be presented. Individual PK parameters will be presented to three significant figures with the exception of T_{max} which will be presented to two decimal places.

- Categorical variables: Descriptive statistics will include counts and percentages per category. The denominator in all percentage calculations will be the number of participants in the relevant analysis population with non-missing data, unless specifically stated otherwise. Percentages will be displayed to one decimal place. Proportions will be displayed to 3 decimal places.

  95% Confidence Intervals (CIs) will be displayed to two decimal place for percentages. Proportions will be displayed to 3 decimal places. P-values will be displayed to 3 decimal places.

- Time to Event Analysis: Through the Kaplan-Meier (KM) method, nonparametric estimates of the survivor function will be represented by quartile estimates (Q1, Median and Q3) along with 95 CIs. Product limit estimates will be presented as part of appendices to the study outputs (SAS output).

  KM plots of estimated survival/failure curves will be produced by cohort.

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings.

- Assessment windows: All assessments will be included in the data listings and no visit windows will be applied to exclude assessments that were performed outside of the protocol specified procedure windows.
- Result display convention: Results will be center aligned in all summary tables and listings. Subject identifiers visit and parameter labels may be left-aligned if required.
- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:

  Date only: YYYY-MM-DD

  Date and time: YYYY-MM-DD HH:MM

If only partial information is available, unknown components of the date or time will be presented as 'NK' (not known), i.e., '2016-NK-NK'. Times will be reported in military time.

3.2 Key Definitions

The following definitions will be used:

- Baseline: The baseline value is defined as the most recent non-missing measurements collected prior to the first study dose. Repeat and unscheduled assessments will be included in the derivation of the baseline values.
- Change from Baseline: The change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit/time point and the baseline value.

  The change from baseline value at each post-baseline visit/time point will be calculated for all continuous parameters using the following formula:

  Change from Baseline Value = Result at Visit/Time Point – Baseline Value

  The change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available and will be treated as missing otherwise.
- Study day: The study day of an event is defined as the relative day of the event starting with the date of the first study drug administration (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the first study drug administration will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration)

  For events occurring on or after Day 1, study day will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration) + 1

  Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

  Relative days compared to an alternative reference point will be calculated similarly, but the alternative starting reference start date will be used instead of the date of the first study drug dosing.

  Study Day in months is calculated as Study Day in days divided by (365.25/12).
- End of study is defined as the date when the last subject, last visit occurs or the date at which all required follow-up data and documentation have been received by Sponsor, whichever occurs later.

3.3 Inferential Analyses

The time to event endpoints will be analyzed using the Kaplan-Meier survival analysis method. The survival functions of the time to event endpoints will be summarized for the 25th percentile, median, and 75th percentile and their 95% confidence intervals.

3.4 Multiple Comparisons and Multiplicity Adjustments.

Not applicable.

3.5 Handling of Missing Data

For the classification of Treatment emergent adverse event (TEAE) and Concomitant medication, the following will be applied in the following order:

a. If all dates/times (start and stop) missing, the event/medication will automatically be classified as a TEAE/Concomitant medication.

b. For AEs with a missing start date/time, if the event end date/time is prior to first study drug administration, the event will not be classified as a TEAE.

c. If only the AE start year/ medication end year is present and is the same or is after the first study drug administration year unit, the event/medication will be classified as a TEAE/Concomitant medication.

d. If the AE start month and year/medication end month and year are present and are the same or after the first study drug administration month and year units, the event/medication will be classified as a TEAE/Concomitant medication.

[redacted]

Conversion of categorical values

In some instances, continuous variables are expressed as a range (i.e. < 10). In such cases, values may be converted to the range boundary (upper or lower limit as applicable). As an example, a value of <10 may be converted to 10. Such substitutions will be clearly documented in the footnotes of relevant outputs.

3.6 Coding of Events and Medications

Medical history and AE verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) using the latest version available at the time of study commencement, graded using NCI-CTCAE version 5.0. Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analysis.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) using the latest version available at the time of study commencement. Medications will be mapped to the full WHO-DD Anatomical Therapeutic Chemical (ATC) class hierarchy, but Anatomical

Therapeutic Chemical (ATC) class Level 3 and preferred name (PN) will be of primary interest in this analysis.

3.7 Cohorts/Stages

- Cohort 1: Checkpoint inhibitor naïve Epstein-Barr Virus (EBV) negative gastric cancer subjects who have progressed on at least 2 prior systemic treatments for advanced or metastatic gastric cancer
    - Stage 1 (at least 10 subjects)
    - Stage 2 (20 subjects + up to additional 30 subjects)

    → Maximum No. of subjects: 60 subjects
- Cohort 2: Checkpoint inhibitor naïve EBV positive gastric cancer subjects who had at least 1 prior systemic treatment for advanced or metastatic gastric cancer
    - Stage 1 (10 subjects)
    - Stage 2 (10 subjects + up to additional 10 subjects)

    → Maximum No. of subject: 30 subjects

4. POPULATIONS FOR ANALYSES

In this study 3 populations for analyses are defined: Treated Set, Evaluable Set, and PK Set.

Furthermore, any additional exploratory analysis not identified in the SAP will be identified in the final CSR as exploratory post hoc analyses, including analyses for additional study populations or subgroups of interest.

4.1 Population Descriptions

4.1.1 Treated Set

All subjects who received at least one dose of study drug (FLX475 or pembrolizumab). All demographics, Baseline characteristics, efficacy and safety data will be analyzed using the Treated Set as a primary analysis population.

4.1.2 Tumor Evaluable Set

All subjects who are enrolled, complete at least one cycle of investigational drug, and is evaluable for tumor response based on RECIST, version 1.1. Tumor Evaluable Set will be used for supportive summaries of efficacy data that related to tumor response.

4.1.3 PK Set

All subjects who received at least one dose of FLX475, and have at least one quantifiable plasma concentrations of FLX475.

PK set will be determined after database lock by the study pharmacometrician and confirmed by Sponsor.

The PK set will be used for all PK concentration data for this study which include concentrations listings, concentrations summary and concentration-time profiles along with plasma PK analysis, the PK parameters listings and summaries, graphical presentation of all PK parameters data if applicable, and statistical analysis of PK parameters if applicable.

5. PARTICIPANT DISPOSITION AND ANALYSIS POPULATIONS

Subject disposition and analysis population analysis will be based on all screened subjects and all enrolled subjects, respectively. Subject disposition and analysis populations will be summarized descriptively as described in section 3.1 (categorical descriptive analysis).

5.1.1 Subject Disposition

Subject disposition will include the number of subjects who was screened, the number of subjects who was enrolled, the number of subjects who completed the study as planned, subjects withdrawn from the study, as well as the primary reason for termination and the primary reason for end of treatment. Subject disposition will be summarized descriptively.

5.1.2 Analysis Populations

The number of subjects included in each study populations will be summarized descriptively, as well as the reason for exclusion.

6. PROTOCOL DEVIATIONS

Protocol deviations will be presented for each subject in the by-subject data listings.

Prior to database lock, all protocol deviations will be reviewed by medical monitors and sponsor.

Protocol deviations (minor) and important protocol deviations (major) will be categorized.

Protocol deviations are tracked within [redacted] Clinical Trial Management System (CTMS).

7. DEMOGRAPHIC AND BASELINE INFORMATION

Demographic and baseline information analysis will be based on the treated set. Demographic and baseline information will be summarized descriptively as described in section 3.1.

7.1 Demographics

The following demographic parameters will be analyzed:

Continuous descriptive analysis:

- Age (years)
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline BMI (kg/m^2)

Categorical descriptive analysis:

- Sex
- Childbearing Potential
- Race

7.2 Medical History

Medical / Surgical history will be coded using MedDRA® and will be presented in the by-subject data listings.

7.3 Oncology History

Oncology history information, including prior cancer disease, current cancer diagnosis, treatment of cancer with systemic cancer therapy/radiotherapy/surgery and best overall response, will be presented in the by-subject data listings. Prior cancer disease will be summarized descriptively as described in section 3.1, as well as current cancer diagnosis and previous cancer treatment.

[redacted]

8. TREATMENT EXPOSURE

Study drug administration results will be presented using the treated set, as well as the data of dose modification. Study drugs include FLX475 and Pembrolizumab.

A by-subject data listing will be generated for study drug administration of FLX475 and will include study drug administration date, time, planned daily dose, and actual daily dose. For Pembrolizumab, this listing will include date of infusion, start time, stop time, planned dose, and actual dose administered.

Treatment exposure will be summarized by cohort for FLX475 and Pembrolizumab. Measures of extent of exposure include the total number of cycles per subject, total cumulative dose per subject, and duration of exposure (days). Dose modification will be summarized as well.

The summary of treatment exposure will also include Relative Dose Intensity (%), which will be calculated as

$$(\text{Actual Dose} / \text{Planned Dose at study start}) \times 100.$$

9. PRIOR/CONCOMITANT MEDICATIONS AND PROCEDURES

Prior medications are defined as all prior medications (including over-the-counter medications) administered within 30 days prior to screening. Concomitant medications are defined as any medications (other than the study drug) administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study treatment. Concomitant surgical and medical procedures are any diagnostic, therapeutic or surgical procedures relating to malignancy during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study treatment.

Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class Level 3 and PN as noted in section 3.1 (categorical descriptive analysis). Subjects who used the same medication on multiple occasions will only be counted once in the specific category (ATC and PN). PNs will be sorted alphabetically. In addition to the summaries by the coded terms, the number of participants who used at least one concomitant medication during the study will be presented.

Prior medications will be presented in the by-subject data listings.

Concomitant surgical and medical procedures will be also presented in the by-subject data listings.

[redacted]

[redacted]

11. PHARMACODYNAMICS

Not applicable.

12. EFFICACY

Efficacy endpoints will be analyzed for the treated set and tumor evaluable set using all tumor assessment results from baseline until the disease progression confirmation or last evaluable tumor assessment before such as start of new anticancer therapy, death, lost to follow-up, etc. Efficacy endpoints will be summarized descriptively as described in Section 3.1 and analyzed as described in Section 3.3.

12.1 Tumor Assessment

Best overall response is the best response recorded from the treatment start date until the earliest of disease progression or last evaluable tumor assessment before events such as start of new anticancer therapy, death, lost to follow-up, etc. Objective response rate (ORR) is defined as the proportion of subjects whose confirmed best overall response is either Complete Response (CR) or Partial Response (PR) according to RECIST version 1.1. Disease control rate (DCR) is defined as the proportion of subjects with confirmed best overall response of CR, PR or SD according to RECIST version 1.1.

The hierarchy used to determine best overall response is CR>PR>SD>PD. [redacted]

The progression date is the earliest date among all images of PD lesion. If a subject does not experience PD in one disease assessment, his/her non-PD date will be the latest date among all images of the disease assessment.

Overall best response categories (including: CR, PR, PD, SD), ORR and DCR will be summarized (categorical descriptive analysis), together with the two-sided exact (Clopper-Pearson) 95% confidence intervals.

Based on the cumulative data about ORR along with prior assumption at each stage, posterior probability of ORR $\geq$ 15% for cohort 1 and ORR $\geq$ 30% for cohort 2 would be computed to determine go/no-go decision of the next stage. This cumulative data analysis will be implemented only if at least one response is observed from stage 1 of each cohort.

According to iRECIST, Best Overall Response (iBOR) of complete response (CR/iCR), partial response (PR/iPR), stable disease (SD/iSD), Progressive disease (iPD) or unevaluable (iUE) will be derived. iORR, iDCR, iTTR, iDoR and iPFS will be analyzed in the same manner as used analyses in accordance with RECIST 1.1. iPD is defined as the time point of first iUPD without subsequent iSD, iPR or iCR before study treatment discontinuation.

For the sum of diameter in target lesion, percent change from baseline at each scheduled tumor assessment time-point and maximal tumor shrinkage from baseline during the study will be summarized.

12.2 Time to Event Endpoints (TTR, DoR, PFS and OS)

The time to event endpoints, including time to response (TTR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS) will be summarized descriptively and graphically by the Kaplan-Meier methodology, as described in Section 3.3.

TTR is defined as the time from the date of first administration of study treatment to first documented CR or PR. DoR is measured from the date of the first observation of tumor response (CR or PR, whichever occurs first) to the date of disease progression or death for the subject with an objective response. PFS is defined as the time from the date of first administration of study treatment to determination of tumor progression by RECIST version 1.1 or death due to any cause, whichever occurs first. OS is defined as the duration of time from the treatment start date to time to death from any cause. If subjects survive at the time of analysis, the subject will be censored at the last date of survival confirmed.

TTR, DoR, PFS, and OS will be calculated in days, as well as in months.

For the tumor-related time-to-event endpoints, subjects who have not experience any event (Progressive Disease (PD) or Death) at the time of analysis will be censored at the date of the last evaluable tumor assessment. However, if the subject progresses or dies after two or more consecutive missed assessments

or start of new anticancer therapy, the subject will be censored at the time of the last evaluable assessment prior to starting new anti-cancer therapy/missed assessments. If the subject has no evaluable baseline/post-baseline assessment, subject will be censored at the date of first administration of study treatment. In case of subjects entering the extension part, the data will be treated as censored at the date of the last evaluable tumor assessment on or before the first administration date in the extension part.

12.3 Sensitivity Analysis

[redacted]

13. SAFETY

Safety endpoints will be analyzed using the treated set. Safety endpoints will be summarized descriptively as described in section 3.1.

13.1 Adverse Events

All AEs including will be coded using the most recent version of the MedDRA coding dictionary, graded using NCI-CTCAE version 5.0.

Treatment emergent adverse events (TEAEs) are defined as adverse events occurring from the first dose of the study treatment through 30 days following cessation of study treatment will be considered 'treatment-emergent'. Adverse events that start before first study treatment and deteriorate under treatment will also be considered as 'treatment-emergent'.

All AE summaries will be restricted to TEAEs only and all the study drug related AE will be summarized [redacted]. Summary tables will include the number of participants (%) experiencing an event and the number of events. Subjects will be counted only once for each SOC and PT level (categorical descriptive analysis). For each TEAE, the most extreme grade recorded in eCRF will be attributed and used in the by-severity summaries.

The TEAE summaries will include:

- Overall summary of TEAEs
- Summary of TEAEs by SOC and PT
- Summary of TEAEs by SOC, PT and Severity
- Summary of SAEs by SOC and PT
- Summary of SAEs by SOC, PT and Severity
- Summary of ECIs by SOC and PT
- Summary of ECIs by SOC, PT and Severity
- Summary of TEAEs Related to (any study drug[redacted]) by SOC and PT
- Summary of TEAEs Related to (any study drug[redacted]) by SOC, PT and Severity
- Summary of SAEs related to (any study drug[redacted]) by SOC and PT
- Summary of TEAEs leading to (any study drug[redacted]) dose modification (reduction / interruption) by SOC and PT
- Summary of TEAEs leading to (any study drug[redacted]) discontinuation by SOC and PT
- Summary of TEAEs leading to death by SOC and PT

Separate by-subject data listings will be created for

- TEAEs
- SAEs
- TEAEs leading to dose modification (reduction/interruption)
- TEAEs leading to drug discontinuation
- TEAEs leading to death
- Adverse events reported prior to treatment but after informed consent

13.2 Safety Laboratory Assessments

Blood and urine samples will be collected at the time points specified in the Schedule of Events (refer to the Protocol) to conduct hematology, serum chemistry, coagulation, urinalysis analyses & microscopic urinalysis, and thyroid function.

The following tests will be performed:

Hematology:

- Hemoglobin
- Hematocrit
- Red Blood Cell Count
- Mean Corpuscular Volume
- Mean Corpuscular Hemoglobin
- White Blood Cell Count
- Neutrophils
- Neutrophils (%)
- Lymphocytes
- Lymphocytes (%)
- Monocytes
- Monocytes (%)
- Eosinophils
- Eosinophils (%)
- Basophils
- Basophils (%)
- Platelets

Serum Chemistry:

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Calcium
- Magnesium
- Phosphorus
- Blood Urea Nitrogen
- Creatinine
- Blood Glucose
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline Phosphatase (ALP)

- Total Bilirubin
- Total Protein
- Albumin
- Lactate dehydrogenase (LDH)
- Amylase
- Uric acid
- Lipase

Coagulation

- Prothrombin Time (PT)
- Activated Partial Thromboplastin Time (aPTT)
- Partial thromboplastin time (PTT)
- International Normalized Ratio (INR)

Urinalysis & Microscopic Urinalysis:

- Bilirubin
- Protein
- pH
- Blood
- Specific Gravity
- Ketones
- Glucose
- Microscopic Examinations

Thyroid Function:

- Triiodothyronine (T3)
- Free triiodothyronine (FT3)
- Free Thyroxine (FT4)
- Thyroid-Stimulating Hormone (TSH)

All laboratory data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

Results for individual parameters may be reported in different units depending on the analyzing laboratory. The results (and the corresponding normal range cut-off values) for individual parameters will be converted to International System of Units (S.I.) units to summarize the data.

For all the parameters where a unit value has been reported, the parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, ‘Albumin (g/L)’. For the urinalysis parameters, the parameter name will be the reported test name only. Parameters will be sorted alphabetically within tables and listings.

For all parameters where a normal range limit value was reported, the normal range will be derived based on the available lower and upper limit values and any reported mathematical symbols. If both a lower and upper limit value is available, the normal range will be presented as ‘(Lower, Upper)’.

The hematology, serum chemistry, coagulation, urinalysis analyses & microscopic urinalysis, and thyroid function results tables will present summary statistics for each laboratory parameter within the specific test panel. For each parameter, summaries will be presented for the baseline and each scheduled post-baseline visit. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit (continuous descriptive analysis).

The decimal precision to which the summaries for each parameter will be based on the maximum number of decimals to which the reported result or the normal range limits are presented to in the raw data. The results and normal ranges will be displayed to the same decimal precision in the listings.

A cross-tabulation of the worst grade that observed in planned and unplanned visits until ED/EOT versus the baseline grade will be presented with shift table for both of the NCI-CTCAE grade and investigator's clinical significance abnormality assessment.

13.3 Vital Signs

The following vital signs measurements will be taken at the time points specified in the Schedule of Events (refer to the Protocol):

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Pulse rate (bpm)
- Respiratory rate (breaths per minutes)
- Temperature (℃)

All vital signs data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Systolic Blood Pressure (mmHg)'. Parameters will be sorted in the order that the measurements were collected in on the Vital Signs eCRF page within the tables and listings.

Vital signs measurements will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit (continuous descriptive analysis).

The decimal precision to which the summaries for each parameter will presented will be based on the maximum number of decimals to which the results were reported on the eCRF.

13.4 12-Lead Electrocardiogram (ECG)

The following ECG measurements will be taken at the time points specified in the Schedule of Events (refer to the Protocol):

- Heart Rate (beats/min)
- PP Interval (msec)
- RR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcB Interval (msec)
- QTcF Interval (msec)

All ECG data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits/time points will be included in the summary tables.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Heart Rate (beats/min)'. Parameters will be sorted in the order that the measurements were transferred from the external vendor [redacted] within the tables and listings.

ECG measurements will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit/time points (continuous descriptive analysis).

Summary of the number and percentage of subjects with average QTcF intervals (< 450ms, 450 – 480 ms, 481 – 500 ms, >= 501 ms) by visit/time point will be provided, as well as summary of the number and percentage of subjects with specific increases from baseline in QTcF intervals (<= 30 ms, > 30 ms, or > 60 ms) by visit/time point.

Since triplicate tracings are done as part of one assessment, the mean of the three tracings per parameter will be summarized for each subject. All values will be listed including the mean value per parameter. Changes from baseline will be calculated based on the mean values of the triplicates where appropriate.

The decimal precision for each parameter will be based on the maximum number of decimals to which the results were reported on the eCRF.

[redacted]

13.5 Physical Examinations

The following body systems will be assessed at the time points specified in the Schedule of Events (refer to the Protocol):

- Head/Ears/Eyes/Nose/Throat
- Chest (Heart and Lungs)
- Abdomen
- Skin
- Neurological
- Neck
- Limbs
- Other

By-subject data listings will be created for height, weight, BMI, all body system results (Abnormal Not Clinically Significant, Abnormal Clinically Significant) and a description of abnormal CS, if applicable.

13.6 Pregnancy Test Results

All information related to pregnancy testing (urine and serum based) will be presented in the by-subject data listings.

13.7 ECOG Performance Status

ECOG performance status results will be presented in the by-subject data listings. A shift table will be generated using the worst (highest) grade until ED/EOT versus baseline ECOG performance status.

13.8 ECHO or MUGA

ECHO or MUGA results will be presented in the by-subject data listings.

14. IMMUNOGENICITY

Not applicable.

15. CHANGES TO THE PLANNED ANALYSIS

Not applicable.

16. INTERIM AND FINAL ANALYSIS

16.1 Interim Analyses

The study is planned initially for 2-stage design for both cohorts but there might be more than 2 stages depending on the results for each cohort. Based on the initial plan with 2-stage design, the interim analysis for each cohort will be performed when the initial 10 subjects of each cohort completes 4 cycles (or 12 weeks; after 2nd response assessment) or withdrawn from the study, whichever occurs first. At this time both efficacy and safety results as well as any available PK and PD data will be reviewed by the IDMC. The number of subjects for the next stage will be determined based on the interim data analysis as well. Study discontinuation due to futility may be recommended by the IDMC to the Sponsor. More details about the decision making based on the interim analysis will be described in charter.

16.2 Final Analysis (End of Study)

The final analysis will be conducted at the time of end of study which was described in the Section 3.2, the clinical database has been locked, and the analysis populations have been approved. As each cohort will enroll target subjects separately and so the analysis will be performed separately for each cohort as well.

The final analysis will be based on the final version of the SAP. Any deviations from the planned analysis will be documented in the CSR.

17. SOFTWARE

- SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

18. TABLES

Table Number	Table Title	Population
[redacted]		

Table Number	Table Title	Population
[redacted]		

Table Number	Table Title	Population
[redacted]		

19. LISTINGS

Listing Number	Listing Title	Population
[redacted]		

Listing Number	Listing Title	Population
[redacted]		

Listing Number	Listing Title	Population
[redacted]		

20. FIGURES

Figure Number	Figure Title	Population
[redacted]		

21. REFERENCES

1) Clinical Study Protocol Version 3.0 dated 6 December 2022.