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Document: Statistical Analysis Plan

Official Study Title:

A Phase 1/2a Open-label, Multicenter, Dose Escalation and Dose Expansion Study of the Safety, Tolerability, and Pharmacokinetics of HPN424 in Patients with Advanced Prostate Cancer Refractory to Androgen Therapy

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Synoptic STATISTICAL ANALYSIS PLAN

HPN424-1001

A Phase 1/2a Open-label, Multicenter, Dose Escalation and Dose Expansion Study of the Safety, Tolerability, and Pharmacokinetics of HPN424 in Patients with Advanced Prostate Cancer Refractory to Androgen Therapy

VERSION 1.0

DATE OF PLAN:

03 March 2023

Harpoon Therapeutics, Inc.
131 Oyster Point Blvd, Suite 300
South San Francisco, CA 94080 USA
Telephone: +1 (650) 443-7300

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2 ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BOR	best overall response
CR	complete response
CRF	case report form
sCSR	Synoptic Clinical Study Report
DLT	dose-limiting toxicity
DODC	duration of disease control
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
MedDRA	Medical Dictionary for Regulatory Activities
mCRPC	Metastatic castrate-resistant prostate cancer
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PR	partial response
PD	progressive disease
PK	pharmacokinetic(s)
PT	Preferred term
PFS	progression-free survival
QTcF	QT interval corrected by Fredericia's formula
RP2D	Recommended phase 2 dose
SAE	Serious adverse events
sSAP	Synoptic Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
SC	Subcutaneous
TEAE	Treatment-emergent adverse event
WHO-DDE B3	World Health Organization Drug Dictionary Enhanced Format B3

3 INTRODUCTION

The purpose of this synoptic statistical analysis plan (sSAP) is to reduce bias by prespecifying the intended analysis methodology, providing comprehensive and detailed documentation of the proposed analysis and reporting, and ensuring clear translations between the clinical objectives and statistical analysis methods.

This sSAP details the planned statistical analysis methods and data presentations for the synoptic clinical study report (sCSR) for the primary analyses for Study HPN424-1001, A Phase 1/2a Open-label, Multicenter, Dose Escalation and Dose Expansion Study of the Safety, Tolerability, and Pharmacokinetics of HPN424 in Patients with Advanced Prostate Cancer Refractory to Androgen Therapy. It was written in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline, E9: Statistical Principles for Clinical Trials (ICH 1998).

This sSAP should be read in conjunction with the study protocol, case report form (CRF), and any other applicable study documents. This sSAP is based on Protocol Amendment 7 Version 8.0 dated 24 September 2021 (UK Version 8.1 dated 01 December 2021, and CRFs from 15 November 2021. Protocol and sSAP revision history is as follows:

sSAP Version	**Protocol Date**	**Protocol Version**
V1.0, 03 March 2023	24 September 2021 01 December 2021 (UK only)	Amendment 7 Version 8.0 Amendment 7 Version 8.1

Analyses will be performed by Harpoon Therapeutics, Inc. using their Standard Operating Procedures.

The derivation and analysis of pharmacokinetic and biomarker endpoints will be discussed in a separate analysis plan.

On 10 March 2022, Harpoon Therapeutics decided to discontinue the study during Part 1 (dose escalation). Part 2 of the study was not initiated. The clinical study report will be a synoptic report focusing on safety data. This sSAP describes the original study objectives and study endpoints but will not summarize any efficacy data, which will only be reported in by-patient listings.

4 STUDY OBJECTIVES AND ENDPOINTS

Protocol objectives and endpoints that are not being addressed in this sSAP are identified with a ~~strikethrough~~.

4.1 Primary Objectives

The primary objectives of this study are:

Dose Escalation: Assess safety and tolerability at increasing dose levels of HPN424 in successive cohorts of patients with metastatic castrate resistant prostate cancer (mCRPC) to estimate the maximum tolerated dose (MTD) or maximum administered dose (MAD) and select the recommended Phase 2 dose(s) (RP2D), and dosing regimen for further investigation.

~~Dose Expansion: Evaluate preliminary clinical efficacy at RP2D(s)~~

4.2 Secondary Objectives

The secondary objectives of this study are:

Dose Escalation:

- Evaluate the overall safety profile of HPN424 administered by intravenous (IV) infusion or subcutaneous (SC) injection
- Characterize single dose and multiple dose PK of HPN424 {see separate PK SAP}
- Evaluate immunogenicity against HPN424 {see separate biomarker SAP}
- ~~Evaluate preliminary clinical anti-tumor activity~~
- Characterize the impact of HPN424 on activation of circulating lymphocytes and systemic soluble immune factors {see separate biomarker SAP}

~~Dose Expansion:~~

- ~~Further characterize the safety and tolerability of HPN424 at the RP2D(s)~~
- ~~Characterize single dose and multiple dose PK of HPN424 at the RP2D(s)~~
- ~~Evaluate immunogenicity against HPN424~~
- ~~Characterize the impact of HPN424 on activation of circulating lymphocytes and systemic soluble immune factors~~

The secondary endpoints for PK and biomarkers underlined above will be addressed in separate SAP(s).

4.3 Primary Endpoints

Dose Escalation:

Number and severity of dose limiting toxicities (DLTs) following treatment with escalating doses of HPN424.

~~Dose Expansion:~~

~~Overall response rate (ORR), as assessed by PCWG3 criteria for response.~~

4.4 Secondary Endpoints

- Adverse events (NCI CTCAE version 5.0).
- Laboratory abnormalities (NCI CTCAE version 5.0).
- ~~Progression-free survival (PFS) using PCWG3 criteria.~~
- ~~Duration of response (DOR) using PCWG3 criteria.~~
- ~~Overall survival (OS).~~
- ~~Change from baseline in PSA over time~~
- ~~Change from baseline in CTCs over time~~
- ~~Pharmacokinetic parameters of HPN424:~~
  - ~~Single dose - maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the single dose concentration-time curve over dosing interval τ ($AUC_{sd,\tau}$), area under the concentration-time curve extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), and clearance (CL) as data permit.~~
  - ~~Multiple dose (assuming steady state is achieved) - maximum concentration at steady state ($C_{ss,max}$), time to maximum concentration ($T_{ss,max}$), area under the steady state concentration-time curve over dosing interval τ ($AUC_{ss,\tau}$), $t_{1/2}$, minimum concentration ($C_{ss,min}$), CL, volume of distribution (V_{ss}), and accumulation ratio ($AUC_{ss,\tau}/AUC_{sd,\tau}$) as data permit.~~
- ~~Incidence and titers of anti-drug antibodies against HPN424.~~
- ~~Pre- and post-dose quantification of soluble cytokines in serum.~~
- ~~Assessment of biomarkers and characterization of immune cell infiltration and activation in the tumor microenvironment~~

5 STUDY DESIGN AND POPULATION

HPN424-1001 is a Phase 1/2a, open-label, multicenter, safety and PK study of HPN424 in adults with histologically or cytologically confirmed adenocarcinoma of the prostate with progressive metastatic disease which, in the opinion of the Investigator, requires initiation of new treatment.

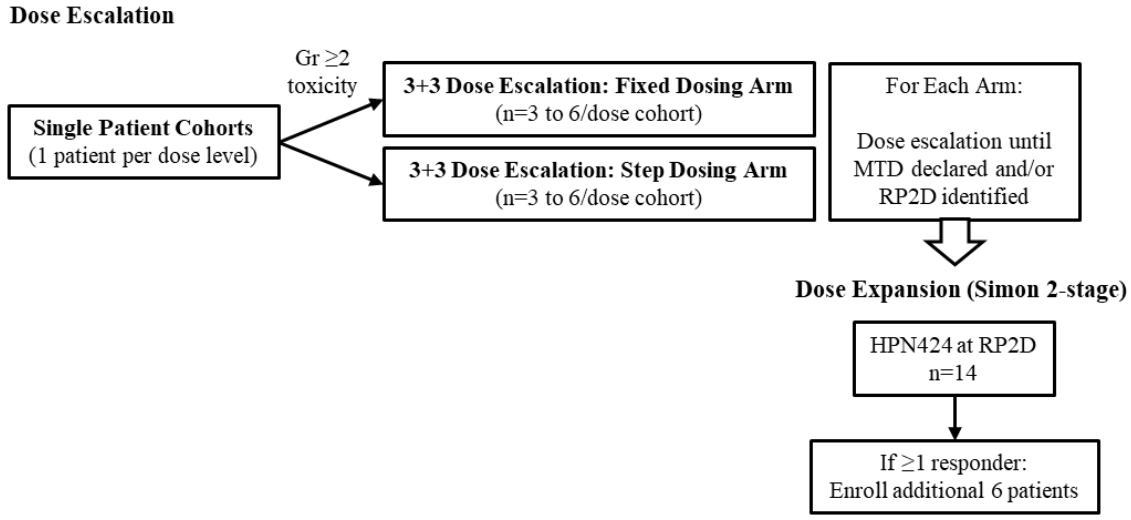
The study was designed to be divided into 2 parts: Dose Escalation and Dose Expansion, however the Dose Expansion portion of the study will not occur. Dose Expansion information in this SAP has been marked with a ~~strikethrough~~ to indicate that it will not occur.

As an added safety measure for this first in human (FIH) trial, single patient cohorts will initially be enrolled and treated. Dose Escalation will then proceed following a 3+3 design to evaluate 2 treatment arms in parallel:

- Fixed Dosing
- Step Dosing

During single patient dose escalation and in the 3 + 3 dose escalation Fixed Dosing arm, patients will receive the Target Dose (the intended dose for a particular cohort) throughout the treatment period. Patients in the Step Dosing arm will initiate treatment with one (or more) Priming Dose(s) followed by the Target Dose level for the duration of treatment.

HPN424-1001 Study Design



HPN424 administered weekly by IV infusion or SC injection

Abbreviations: DLT = dose-limiting toxicity (per protocol); MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose; toxicity = AEs related or suspected to be related to HPN424, except those judged not to present safety risk

For each treatment arm, Dose Escalation will continue until the MTD is declared, RP2D(s) are identified, or the Sponsor decides to stop enrollment in one or more arms. A Cohort Review Committee (CRC) comprised of selected Investigators and Sponsor representatives including the

Medical Monitor will monitor safety throughout the trial. Following completion of the DLT period for all patients in a given dose cohort, the CRC will review the safety, clinical activity, and any available PK and pharmacodynamic data prior to opening the next higher dose level.

During Dose Escalation, additional patients may be enrolled and treated at dose levels previously determined to be safe by the CRC, ie, backfilling previously cleared dose levels, after review and approval by the Sponsor. For example, these backfill cohorts may explore intermediate or lower dose levels, different priming dose levels, different schedules (e.g., split-dosing), or modified premedication use based on emergent safety and available PK data.

Patients actively receiving therapy may be considered for intra-patient dose escalation to receive a dose level no higher than the highest dose that has previously been deemed safe and tolerable (and thus below the MTD) by the CRC, following review and approval by the Medical Monitor.

HPN424 will be administered by either intravenous (IV) infusion or subcutaneous (SC) injection. All patients will be administered HPN424 once weekly (QW) during 21-day cycles. Pre-medications will be administered as indicated based on assigned cohort.

Patients may continue to receive HPN424 treatment beyond disease progression provided there is clinical benefit (NLCB, per PCWG3 guidelines) as determined by the Investigator and upon consultation with the Medical Monitor. Disease assessments (PSA, bone scans and CT/MRI) should continue irrespective of whether study treatment is missed or delayed.

5.1 Schedule of Assessments

Patient participation includes Screening (28 days), Treatment (ongoing in 21-day cycles), an End of Treatment visit (within 7 days after the last dose of HPN424), and Safety Follow-up (SFU; ≥28 days [+7 days] after the last dose of HPN424), after which patients will enter long term follow-up (LTFU) for survival. Patients may continue weekly HPN424 treatment as long as they are receiving clinical benefit (as determined by the Principal Investigator and upon consultation with the Sponsor Medical Monitor).

Schedules of visits and assessments conducted throughout the study are dependent on the assigned dosing regimen and route of administration, and are detailed in the following protocol appendices:

- Appendix 1: Fixed Dose Intravenous Regimen
- Appendix 2: Step Dosing Intravenous Regimen
- Appendix 3: Fixed Dose Subcutaneous Regimen

5.2 Sample Size Determination

Up to 150 patients with mCRPC may be enrolled. The number of cohorts and patients will depend on data observed during Dose Escalation.

Dose Escalation may include up to 130 patients, depending on the dose at which the MTD and RP2D(s) are determined. The sample size and design of the Dose Escalation portion of the study are consistent with those in other oncology studies used to determine MTD. The traditional 3 + 3

dose escalation scheme employs the standard NCI definition of MTD (highest dose associated with DLT in <33.3% of patients) for each arm.

~~Dose Expansion will include up to 20 evaluable patients using a Simon 2-stage design to assess preliminary clinical efficacy of HPN424 at the RP2D(s). Power calculations based on a Simon 2-stage minimax design test the null hypothesis that overall response rate (ORR) ≤0.01 versus the alternative hypothesis that ORR ≥0.15, with a Type 1 error rate of 0.05 and power of 80%. This design would allow identification of a target response rate of 15% or better in a population of patients who have failed standard available therapy and would not be expected to have any responders.~~

~~A sample size of 14 evaluable patients will be enrolled in the first stage. If the total number responding (defined as partial response [PR] or complete response [CR] is ≥1, an additional 6 evaluable patients will be enrolled in the second stage for a total of 20 evaluable patients. If the total number responding is ≤1, the effectiveness of treatment based on ORR will be rejected. If treatment is actually not effective and ORR ≤0.01, then the expected sample size is 14.8 evaluable patients with a 0.869 probability of early termination and there is a 0.016 probability of incorrectly concluding the treatment is effective (the target for this Type 1 error rate was 0.05 or less). If the treatment is actually effective, there is a 0.199 probability of incorrectly concluding it is not effective (the target for this Type 2 error rate was 0.20 or less).~~

~~While the intention is to study a single RP2D, additional expansion cohorts of up to 20 patients per expansion cohort may be added at the recommendation of the CRC. If the CRC recommends multiple RP2Ds, each will be evaluated with independent Simon 2-stage designs of up to 20 evaluable patients per RP2D.~~

5.3 Interim Analysis

No formal interim analyses are described in the protocol and none are planned. In Part 1, all available data will be reviewed to enable dose-escalation and dose selection decisions. Except for the occurrence of a MTD, there are no stopping rules described in the protocol.

A review of safety data, clinical activity, and any available PK and pharmacodynamics data will be conducted upon completion of each dose escalation cohort by the Cohort Review Committee (CRC). Additionally, a Study Safety Oversight Committee (SSOC) will review safety quarterly, including at the identification of any DLT, and will make recommendations to the CRC.

5.4 Timing of Analyses

~~Part 2 Dose Expansion of the study will be conducted in up to 2 stages. After testing the treatment on 14 evaluable patients in the first stage, the data will be analyzed and the study will be terminated if no (0) patients have a response (CR or PR). If at least 1 patient responds, an additional 6 evaluable patients will be enrolled in the second stage for a total of 20 evaluable patients.~~

~~The primary analysis will be conducted after all patients have completed at least 6 cycles of treatment or discontinued study treatment and completed the End of Treatment visit. A~~

~~supplemental analysis may be completed at the end of study that includes the cumulative data collected after the final analysis (i.e., through SFU).~~

On 10 March 2022, Harpoon Therapeutics decided to discontinue the study during Part 1 (dose escalation). Part 2 (dose expansion) of the study was not initiated. The clinical study report will be a synoptic report focusing on safety data. This sSAP describes the original study objectives and study endpoints but will not summarize any efficacy data, which will only be reported in by-patient listings.

5.5 Sources of Data

Data management of this study is being conducted with a contract research organization (CRO) using Medidata RAVE electronic data capture (EDC). All data management activities are handled under the SOPs of the CRO.

Protocol deviations were provided by Clinical Research from the clinical trial management system (CTMS).

Adverse event data is reported from the EDC only. The SAE database was used to reconcile the EDC adverse event database but is not included in any analyses.

6 DATA ANALYSIS CONSIDERATIONS

All analyses will be conducted using SAS® version 9.4 or higher.

All relevant clinical data collected in the electronic data capture (EDC) database will be presented in by-patient data listings, including any derived fields used in analyses. All listings will be sorted by study part, cohort, patient ID, and assessment date (and time, if available).

Descriptive summaries of continuous data will generally include the number of patients, mean, median, standard deviation, and minimum and maximum values. Descriptive summaries of categorical data will generally include the number of patients, count, and percentage based on the number of non-missing values. If one or more patients are missing data, the number of missing values will be presented as a separate category with no percentage. Counts of 0 will be presented without percentages.

No p-values will be derived for this Phase 1/2a study.

Data will be reported with the following precision:

- Mean, median: 1 additional decimal place to that reported in raw data
- Standard deviation: 2 additional decimal places to that reported in raw data
- 95% CIs: 2 additional decimal places to that reported in raw data
- Minimum, maximum: same precision to that reported in raw data
- Percentages: 1 decimal place

Patients who withdraw or are lost to follow-up will be included in statistical analyses to the point of their last evaluation.

6.1 Randomization and Blinding

This is not a randomized study. All study treatment will be administered open-label. Study patients, study center personnel, and Harpoon will not be blinded to study treatment or clinical data.

6.2 Stratification and Covariates

No stratification is planned for this study, and no covariate-adjusted analyses will be performed.

6.3 Analysis Sets

Patients will be summarized based on their assigned dose cohort. The following analysis sets will be used for this study:

- ***Safety Population:*** All enrolled patients who receive any amount of HPN424 study treatment.

6.4 Evaluation of Subgroups

No subgroup analyses are planned.

6.5 Multiple Comparisons and Multiplicity

The statistical analyses of data are descriptive in nature. Therefore, no adjustments for multiple comparisons or multiplicity are planned.

7 GENERAL DATA HANDLING CONVENTIONS

7.1 Data Display Characteristics

All data collected in EDC will be reported in by-patient data listings, including any derived variables. They will be sorted by cohort, patient number, and date/time of assessment. The data will include all patients in the database regardless of their receipt of study drug.

Part 1 of the trial has too many dose cohorts to reasonably fit on a single summary table. Since the primary goal of data review and reporting will be focusing on the major differences in dosing schedule, the goal will be to group the dose escalation cohorts. As a result, the following groupings of data will apply to table headers to summarize data in all demographic and safety tables:

- Fixed dose IV cohorts (cohorts 1 – 12)
- Step-dosing IV cohorts who received a single prime followed by the target dose (step cohorts 1, 301, and 302)
- Step-dosing IV cohorts who received two prime doses followed by the target dose (step cohorts 501 – 504)
- Fixed dose SC cohorts (cohort 701)

Summary tables will generally present the dosing cohorts as shown below.

Safety Tables

Parameter	Fixed IV	1 Prime Step IV	2 Prime Step IV	Fixed SC	Study Total

Specific study cohorts and treatment dose levels are as follows:

Study Part	Cohort Number	HPN424 Dose Levels
Dose Escalation Fixed Dosing IV	1	1.3 ng/kg IV
	2	4 ng/kg IV
	3	12 ng/kg IV
	4	24 ng/kg IV
	5	30 ng/kg IV
	6	40 ng/kg IV
	7	54 ng/kg IV
	8	72 ng/kg IV
	9	96 ng/kg IV
	10	120 ng/kg IV
	11	160 ng/kg IV
	12	150 ng/kg IV
Dose Escalation 1 Prime	1	12 / 36 ng/kg IV
	301	100 / 300 ng/kg IV

Study Part	Cohort Number	HPN424 Dose Levels
Step Dosing IV	302	75 / 225 ng/kg IV
Dose Escalation 2 Prime Step Dosing IV	501	100 / 300 / 450 ng/kg IV
	502	50 / 150 / 300 ng/kg IV (prior chemo)
	503	50 / 150 / 300 ng/kg IV (no prior chemo)
	504	50 / 150 / 450 ng/kg IV
Dose Escalation Fixed Dose SC	701	120 ng SC

Patients will be reported in their original dose cohort, regardless of any intra-patient dose escalation or dose changes. No patient on study received both IV and SC dosing.

7.2 Definitions of Study Day, Durations, Baseline, and Post-Baseline Changes

Study day will be based on the date of administration of the first dose of HPN424 study treatment. Date calculations for any duration outcomes will be defined as follows:

- date of interest – first dose date + 1, when the date of interest is on or after the first dose date
- date of interest – first dose date, when the date of interest is before the first dose date

Study Day 1 is defined as the day the first dose of HPN424 study treatment is administered.

Duration outcomes will generally be reported in days. When necessary to convert to weeks, the duration in days will be divided by 7. When necessary to convert to months, the duration in days will be divided by 30.4375. When necessary to convert to years, the duration in days will be divided by 365.25.

Baseline will be based on the last non-missing value collected before or on the date (and time, if applicable) of the first dose of HPN424 study treatment. Post-baseline values will be those collected after the first dose of study treatment.

Change from baseline is defined as: post-baseline value – baseline value.

Percentage change from baseline is defined as:
[(post-baseline value – baseline value) / baseline value] x 100%

7.3 Imputation of Partial Dates and Missing Values

Data will not be imputed for analyses, with the exceptions noted below. These imputations will not change the raw data and will not change the data reported in listings. They will be used for analysis purposes only.

Date of diagnosis (years since initial diagnosis)

- If the year is missing, no imputation will be conducted.
- If the month is missing, the month will be set to January.
- If the day is missing, the day will be set to 1.

Adverse Events (to identify treatment emergence)

- If any part of the start date (month, day, year) is missing, no date imputation will be conducted. An adverse event (AE) with a partial date where the event could have occurred on or after the study treatment start date will be considered treatment emergent.

8 STUDY PATIENT DATA

8.1 Patient Enrollment

The number of patients treated by country and study site, including the name and institution of each investigator, will be summarized.

8.2 Patient Disposition

Patient disposition summaries will include the number of patients receiving study drug, the reasons for study treatment termination, the reasons for study discontinuation, and time on study in months.

8.3 Protocol Deviations

Protocol deviations will be identified by the Investigator and/or Harpoon as major and minor and classified by type before the database is locked. The patient incidence of major protocol deviations will be summarized for Safety Population overall and by the following major categories:

- inclusion and/or exclusion criteria (those who entered the study even though they did not satisfy the entry criteria)
- withdrawal criteria (those who developed withdrawal criteria during the study but were not withdrawn)
- study drug or dosing criteria not met (those who received the wrong treatment or incorrect dose or dosing error [modify as appropriate if only doses outside certain limits are considered major treatment deviations])
- concomitant medication/therapy (those who received a prohibited concomitant treatment)
- informed consent (those from whom informed consent was not properly obtained)
- deviations attributed to COVID-19

8.4 Demographic and Baseline Disease Characteristics

Demographics and baseline disease characteristics summaries will be provided for the Safety Population. Patient demographics, including age (in years) at consent, race, ethnicity, baseline body mass index (BMI) (in kg/m^2), and baseline body surface area (BSA) (in m^2), will be summarized using descriptive statistics. Age as a categorical variable (< 65 or ≥ 65 years) will also be summarized.

The following conversions and equations will be used as applicable:

- Height (in cm) = height (in inches) × 2.54
- Weight (in kg) = weight (in lbs) × 0.4536
- BMI (kg/m^2) = weight (kg) ÷ (height $(m)^2$)
- BSA (m^2) = $\sqrt{[(\text{height (cm)} \times \text{weight (kg)}) \div 3600]}$

Disease characteristics at baseline will be summarized using descriptive statistics and will include the following:

- ECOG performance status at baseline

- time from initial diagnosis of cancer (in months)
- metastatic disease site
- TNM classification at diagnosis
- received bisphosphonates
- pharmacologically castrate (yes/no)
- surgically castrate (yes/no)
- sum of target lesions per RECIST 1.1 at baseline (mm)
- baseline predictive laboratory tests including testosterone, alkaline phosphatase, PSA, LDH, and hemoglobin

Prior cancer therapy at screening will be summarized using descriptive statistics and will include the following:

- total number of prior systemic therapies
- prior systemic therapies by category
  - next generation AR
  - ADT
  - Immunotherapy
  - Immune checkpoint inhibitor
  - Chemotherapy in the hormone-sensitive setting
  - Chemotherapy in the castrate-resistant setting
  - Any chemotherapy
  - Bone-targeted therapy
  - PSMA targeted
  - PARP inhibitor
  - TKI
  - Radiopharmaceutical
  - Other
- best response to most recent systemic therapy
- prior radiation therapy (yes/no) and type
- prior cancer surgery (yes/no) and type

8.5 Medical History

General medical and surgical history will be provided in a by-patient data listings only.

8.6 Prior and Concomitant Medication

All medications will be coded to WHO Drug Dictionary Anatomical Therapeutic Chemical (ATC) classification and preferred name (WHO-DDE B3). At the time of database lock, the latest version of WHO-DDE will be used to code all medications. The WHO-DDE version

number will be reported in footnotes in the concomitant medication listing and described in the study report.

Prior medications are those received before the first dose of study drug or who have a partial date that suggests the drug was begun prior to the first dose of study drug. Concomitant medications are those received at any point after first dose of study drug. Pre-dose medications are those prescribed in the protocol to be received by the patient prophylactically prior to administration of HPN424. These include dexamethasone, diphenhydramine, acetaminophen, non-steroidal anti-inflammatories, and anti-emetics. All medications reported on the pre-med CRF will be included as pre-dose medications.

Prior and concomitant medication data, including pre-meds, will be provided in by-patient data listings only.

9 EFFICACY

All efficacy data will be reported only in by-patient data listings.

Best overall response (BOR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), and change from baseline in PSA are all secondary endpoints for Part 2 Dose Escalation. Duration of disease control (DODC) is an additional exploratory endpoint for this study.

All efficacy endpoints derived from tumor imaging and response assessments are determined by the investigator using Prostate Cancer Working Group Criteria 3 (PCWG3). Evaluations of overall response are identified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE).

9.1 Efficacy Endpoints

9.1.1 Best Overall Response (BOR)

A patient's BOR is defined as the best disease response assessed during the study given a hierarchy of overall response results (CR > PR > SD > PD > NE). BOR will be based on assessments collected after the first dose of study drug until disease progression is documented. Assessments collected after the start of new cancer treatment will not be considered. Confirmation of a response is not required for BOR. Patients who do not have post-baseline assessments will be considered non-responders.

9.1.2 Progression-Free Survival (PFS)

PFS is defined as the time from first dose of study drug to first documentation of disease progression or death due to any cause. Patients who do not experience progressive disease and are alive will be censored at the time of last evaluable tumor assessment. See Section 13.2 for detailed PFS censoring rules.

9.1.3 Duration of Response (DOR)

DOR is defined as the time from the first tumor assessment that supports the patient's objective disease response (CR, PR) to the time of disease progression or death due to any cause. DOR will be computed only for patients who have been identified as responders during the study.

9.1.4 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. For patients who are lost to follow up, the last visit in the database or last contact date when the patient is documented to be alive will be used as the last known date alive.

9.1.5 Change from Baseline in PSA

PSA testing was conducted at local laboratory facilities at each site and entered into EDC as per the protocol schedule.

By-patient data listings will be provided reporting the change from baseline over time for all patients with non-missing data at baseline, including the maximum percent change from baseline.

9.1.6 Duration of Disease Control (DODC)

DODC is defined as the time from the first tumor assessment that supports the patient's disease control (CR, PR, SD) to the time of disease progression or death due to any cause. DODC will be computed only for patients who have been identified as having disease control during the study.

10 SAFETY

All safety analyses will be based on the Safety Population.

10.1 Study Drug Exposure and Compliance

A summary of HPN424 study drug exposure and compliance will be provided. The number of cycles of administration (of any dose within the cycle) of HPN424 will be reported as continuous and categorical outcomes (e.g., by cycle). Total infusions, total dose received, total dose planned, and treatment duration in weeks will be summarized. Total number of dose modifications and reasons for modification will be summarized.

10.2 Adverse Events

Verbatim AE terms will be coded based using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 for reporting by System Organ Class (SOC) and Preferred Term (PT). The MedDRA version number will be reported in footnotes on each AE table and described in the study report.

The severity of AEs is graded by the Investigator according to the NCI CTCAE version 5.0, with the exception of CRS, which was graded by ASTCT criteria.

Treatment-emergent adverse events (TEAEs) are defined as all events that occur or worsen in severity during or after the first HPN424 study drug administration through 28 days after the last dose of study drug. In addition, any event that occurs after this time period is reported as a TEAE if the event is assessed by the investigator as related to study drug.

An overall summary of TEAEs will be provided that includes the patient incidences (numbers and percentages) by cohort and overall of the following categories of events:

- TEAEs
- TEAEs related to study drug
- NCI CTCAE Grade 3 or higher TEAEs
- NCI CTCAE Grade 3 or higher TEAEs related to study drug
- Treatment-emergent SAEs
- Treatment-emergent SAEs related to study drug
- Dose limiting toxicities (DLTs)
- CRS or IRR TEAEs
- TEAEs that lead to study drug discontinuation
- TEAEs related to study drug that lead to study drug discontinuation
- TEAEs that lead to dose reduction or interruption
- TEAEs related to study drug that lead to dose reduction or interruption
- Fatal TEAEs
- Fatal TEAEs related to study drug

The patient incidence by cohort of each of the above categories of TEAEs will be summarized separately by SOC and PT. Multiple TEAEs will be counted once per patient within each SOC and each PT. For TEAE summaries, multiple TEAEs will be counted once per patient at the

maximum severity NCI CTCAE grade reported within each SOC and each PT. Tables will be sorted by SOC and PT frequency in descending order of overall incidence.

An additional patient incidence summary will be provided sorted by PT showing TEAEs with an overall patient incidence rate > 10%.

Non treatment-emergent adverse events will be included only in the by-patient data listings.

10.3 Cytokine Release Syndrome (CRS) and Infusion Related Reactions (IRR) AEs

Cytokine Release Syndrome (CRS) and Infusion Related Reactions (IRR) are considered adverse events of clinical interest. CRS symptoms were collected in a separate module in EDC to more accurately capture timing and severity of each symptom associated with CRS.

Unlike all other AEs, CRS was graded according to ASTCT criteria (Lee, 2019), a more detailed grading system designed for CAR-T cell and immune effector cell therapies. Prior to October 2021 (protocol Amendment 6), CRS was graded according to Lee 2014 criteria. The primary difference between the two grading systems is the inclusion (Lee 2014) vs exclusion (ASTCT) of organ toxicity in grading CRS. ASTCT focuses on the extent of hypotension and hypoxia, and organ toxicity is graded separately. Legacy CRS grades were re-assessed by the site and updated in EDC to ASTCT grade as required.

For CRS only, all AE summary tables will report the ASTCT grade rather than NCI CTCAE grading. Tables will be footnoted to ensure clarity:

- All adverse events are graded according to NCI-CTCAE v5.0 except Cytokine Release Syndrome, which is graded according to ASTCT

In addition to the described AE tables and to ensure they are captured consistently, CRS symptoms will be summarized separately showing incidence of symptoms from the CRS symptom page.

10.4 Deaths

The numbers and percentages of patients who died overall (ie, including survival follow-up and publicly available data for patients lost to follow-up) and within 28 days of last dose of study drug will be summarized. The summary will also include the reported causes of death.

10.5 Safety Laboratory Assessments

Routine hematology, serum chemistry, and coagulation parameters will be converted from the institution's local laboratory results and reported based on the International System of Units (SI). Textbook normal ranges will be used when local laboratory ranges are not available. Safety laboratory reporting specifications are described in Section 13.3. NCI CTCAE laboratory toxicity grading is described in Section 13.4. Note that toxicity grading is based exclusively on quantitative laboratory results and does not include clinical interpretation. When CTCAE grades have overlapping laboratory ranges and are differentiated based on clinical assessment, the higher grade is assigned. All tables and listings that report safety laboratory grades should contain the footnote:

See Statistical Analysis Plan Sections 13.3 and 13.4 for details regarding laboratory grading

The following summaries of hematology, and serum chemistry, and coagulation parameters will be provided by treatment group and overall, for all NCI-CTCAE graded parameters:

- Shifts from baseline NCI CTCAE grade to maximum post-baseline NCI CTCAE grade

Urinalysis data will be provided in a by-patient data listing only.

A by-patient data listing of patients who have laboratory values that meet Hy's Law criteria will be provided.

10.6 Electrocardiograms (ECG)

ECG parameters include heart rate (bpm), PR interval (ms), QRS duration (ms), QT interval (ms), and QT interval corrected by Fredericia's formula (QTcF) (ms). Any triplicate results collected on the ECG CRF will be averaged. ECGs will be interpreted by the Investigator as normal; abnormal, not clinically significant; or abnormal, clinically significant.

If QTcF interval results are not provided on the CRF, the interval will be calculated as:

$$\text{QTcF interval} = QT/RR^{0.33} \quad \text{(where RR} = 60 \div \text{heart rate)}$$

The numbers and percentages of patients with maximum post-baseline QTcF interval values and maximum changes in QTcF interval values from baseline in the categories below will be summarized.

Absolute QTcF interval

- QTcF interval > 450 ms
- QTcF interval > 480 ms
- QTcF interval > 500 ms

Change from baseline in QTcF interval:

- QTcF interval increase from baseline > 30 ms
- QTcF interval increase from baseline > 60 ms

10.7 ECOG Performance Status

ECOG Performance Status results will be provided in a by-patient data listing.

10.8 Vital Signs

Vital signs collected include pulse rate (bpm), temperature (^{o}C), systolic and diastolic blood pressure (mmHg), and pulse oximetry (%). Weight (kg) also was collected and will be presented with vital signs. A by-patient data listing will be provided.

10.9 Physical Examinations

Physical examination data will be provided in a by-patient data listing.

11 CHANGES TO THE PLANNED ANALYSIS

Additional details have been provided for analysis and data presentations described in the protocol, but no changes were made to the analyses specified in the protocol. Any deviations from the final approved sSAP will be described and justified in the sCSR.

12 REFERENCES

FDA. 2009. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation.

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13 APPENDICES

13.1 List of Planned Tables and Listings

All tables and listings will be numbered according to ICH E3 Guidelines.

Tables:

14.1 = demographic data

14.3 = safety data, with:

14.3.1 = adverse events

14.3.2 = listings of deaths, other serious and significant adverse events

14.3.3 = narratives of deaths, other serious and significant adverse events

14.3.4 = abnormal laboratory values

14.3.6 = study drug exposure

Listings:

16.2.1 = discontinued patients

16.2.2 = protocol deviations

16.2.4 = demographic data

16.2.5 = compliance and/or drug concentration data

16.2.6 = individual efficacy response data

16.2.7 = adverse events

16.2.8 = individual laboratory measurements

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Table Number	Description
14.3.3	Summary of Deaths
14.3.4.1	Safety Laboratory Assessment Shift Table – Serum Chemistry Change from Baseline to Maximum Post-Baseline NCI CTCAE Grade
14.3.4.2	Safety Laboratory Assessment Shift Table – Hematology Change from Baseline to Maximum Post-Baseline NCI CTCAE Grade
14.3.4.3	Safety Laboratory Assessment Shift Table – Coagulation Change from Baseline to Maximum Post-Baseline NCI CTCAE Grade
14.3.4.4	Safety Laboratory Assessment Summary of Patients with Post-Baseline NCI CTCAE Grade 3 or Higher
14.3.5	Summary of 12-Lead Electrocardiogram Abnormalities and Potential QTcF Interval Prolongation
14.3.6	Study Drug Exposure and Compliance

Table of Contents - Listings

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16.2.2	Patient Enrollment and Eligibility (Inclusion / Exclusion)
16.2.3	Protocol Deviations
16.2.4.1	Demographics
16.2.4.2	Prostate Cancer Medical History
16.2.4.3	Prior Anticancer Therapy
16.2.4.4	Prior Radiation Therapy
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16.2.4.6	Medical History
16.2.5.1	HPN424 Administration
16.2.5.2	HPN424 Infusion Interruptions
16.2.5.3	Hospital Admission
16.2.6.1	Overall Efficacy Endpoints
16.2.6.2	Radiographic Scans
16.2.6.3	Target Lesions
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16.2.6.5	New Lesions
16.2.6.6	Bone Scan Assessment
16.2.6.7	Overall Disease Assessment

Listing Number	Description
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16.2.7.2	Serious Adverse Events
16.2.7.3	Dose-limiting Toxicities
16.2.7.4	Adverse Events Leading to Treatment Discontinuation
16.2.7.5	Adverse Events Leading to HPN424 Dose Modifications
16.2.7.6	Fatal Adverse Events
16.2.7.7	Cytokine Release Syndrome / Infusion Related Reactions Symptoms
16.2.7.8	Deaths
16.2.8.1	Laboratory Results: Hematology
16.2.8.2	Laboratory Results: Chemistry and Testosterone
16.2.8.3	Laboratory Results: Coagulation
16.2.8.4	Laboratory Results: Urinalysis
16.2.8.5	NCI CTCAE Grade 3 or Higher Laboratory Results
16.2.8.6	Patients who had laboratory values that Meet Criteria for Hy's Law
16.2.8.7	Central Laboratory Sample Collection
16.2.8.8	Serum Cytokines – Local Lab
16.2.9.1	12-Lead ECG
16.2.9.2	Vital Signs
16.2.9.3	ECOG Performance Status
16.2.9.4	Physical Examination
16.2.10.1	Prior and Concomitant Medications and Pre-meds
16.2.10.2	Concomitant Procedures
16.2.11.1	Safety Follow-Up
16.2.11.2	Survival Status / Long Term Follow-Up Status

13.2 Progression-free Survival Censoring Rules

(Censor for new anti-cancer therapy but not for treatment withdrawals.)

Situation	Date of Progression or Censoring	Outcome
Death before first assessment visit	Date of death	Progressed
No Baseline tumor assessments	Day 1	Censored
Death or progression after more than one missed assessment before switch to other anti-cancer therapy	Date of last radiological assessment of measured lesions	Censored
Progression documented before switch to other anti-cancer therapy	Earliest of the following assessed before switch to other anti-cancer therapy: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Death between adequate assessment visits before switch to other anti-cancer therapy	Date of death	Progressed
Switch to other anti-cancer therapy.	Date of last radiological assessment of measured lesions prior other anti-cancer therapy	Censored
No progression before switch to other anti-cancer therapy	Date of last radiological assessment of measured lesions	Censored

Source: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, Appendices C and D

13.3 Safety Laboratory Reporting Specifications

Laboratory Test **Full Name**	**Abbreviation**	**Reported Units (SI)**	**Sort Order [1]**	**CTCAE v5.0 Grading [2]**	**Decimal places**	**Textbook Normals / Source [3]**
Hematology						
Hemoglobin	Hgb	g/L	1	Dec [*1,2,3*] / Inc [1,2,3] **[4]**	0 (XXX)	120 – 160 (female) 140 – 170 (male)
Hematocrit	Hct	L/L	2	-	2 (0.xx)	0.36 – 0.47 (female) 0.41 – 0.51 (male)
Red Blood Cell Count (Erythrocytes)	RBC	10^12/L	3	-	1 (X.x)	4.2 – 5.9
Platelet Count	Plt	10^9/L	4	Dec	0 (XXX)	150 - 350
White Blood Cell Count (Leukocytes)	WBC	10^9/L	5	Dec / Inc [*3*]	1 (XX.x)	3.9 – 10.7
Neutrophils	ANC	10^9/L	5.1	Dec	1 (XX.x)	1.8 – 8.5 (from JAMA)
Lymphocytes	Lymph (abs)	10^9/L	5.2	Dec / Inc [*2,3*]	1 (XX.x)	1.0 – 4.8 (from JAMA)
Monocytes	Mono (abs)	10^9/L	5.3	-	1 (XX.x)	0.0 – 0.8 (from JAMA)
Eosinophils	Eos (abs)	10^9/L	5.4	Inc [*1*]	1 (XX.x)	0.0 – 0.45 (from JAMA)
Basophils	Baso (abs)	10^9/L	5.5	-	1 (XX.x)	0.0 – 0.2 (from JAMA)
Neutrophils	Neut (%)	%	N/A*	-	1 (XX.x)	20 – 59 (from JAMA)
Lymphocytes	Lymph (%)	%	N/A*	-	1 (XX.x)	10 – 34 (from JAMA)
Monocytes	Mono (%)	%	N/A*	-	1 (XX.x)	2 – 4 (from JAMA)
Eosinophils	Eos (%)	%	N/A*	Inc [*1*]	1 (XX.x)	0 – 2.7 (from JAMA)
Basophils	Baso (%)	%	N/A*	-	1 (XX.x)	0 – 0.3 (from JAMA)
Chemistry – Electrolytes						
Carbon Dioxide	CO2	mmol/L	1	-	0 (XX)	23 – 28
Calcium	Calc	mmol/L	2	-	1 (X.x)	2.2 – 2.6
Corrected calcium (serum calcium) **[5]**	CalcCor	mmol/L	3	Dec / Inc	1 (X.x)	2.2 – 2.6

Laboratory Test Full Name	Abbreviation	Reported Units (SI)	Sort Order [1]	CTCAE v5.0 Grading [2]	Decimal places	Textbook Normals / Source [3]
Chloride	Chlor	mmol/L	4	-	0 (XXX)	98 – 106
Magnesium	Magnes	mmol/L	5	Dec / Inc [*1,3,4*]	2 (X.xx)	0.62 – 0.99
Phosphorus	Phos	mmol/L	6	-	2 (X.xx)	0.97 – 1.45
Potassium	Pot	mmol/L	7	Dec [*1,3,4*] / Inc	1 (X.x)	3.5 – 5.0
Sodium	Sod	mmol/L	8	Dec [*1,3,4*] / Inc	0 (XXX)	136 – 145
Chemistry – Hepatic						
Total Protein	TProt	g/L	1	-	0 (XX)	60 - 78
Albumin	Alb	g/L	2	Dec [*1,2,3*]	0 (XX)	35 – 55
Globulin	Glob	g/L	3	-	1 (XX.x)	25 – 35
Alkaline Phosphatase	ALP	U/L	4	Inc	1 (X.x)	36 – 92
Bilirubin Total	TBili	umol/L	5	Inc	1 (XX.x)	5.1 – 20.5
Bilirubin Direct	DBili	umol/L	6	-	1 (XX.x)	0.0 – 5.1
Alanine Aminotransferase	ALT	U/L	7	Inc	2 (X.xx)	0 – 35
Aspartate Aminotransferase	AST	U/L	8	Inc	2 (X.xx)	0 – 35
Chemistry – Renal						
Blood Urea Nitrogen **[6]**	BUN	mmol/L	1	-	1 (X.x)	2.9 – 7.1
Urea **[6]**	Urea	mmol/L	2	-	1 (XX.x)	2.9 – 9.4
Creatinine	Creat	umol/L	3	Inc	0 (XXX)	61.9 – 115
Chemistry – Other						
Glucose **[7]**	Gluc	mmol/L	1	Dec	1 (XX.x)	3.9 – 5.8 (fasting)
Lactate Dehydrogenase	LDH	U/L	2	Inc	2 (X.xx)	60 – 160
Amylase	Amylase	U/L	3	Inc	2 (X.xx)	0 – 130

Laboratory Test Full Name	Abbreviation	Reported Units (SI)	Sort Order [1]	CTCAE v5.0 Grading [2]	Decimal places	Textbook Normals / Source [3]
Lipase	Lipase	U/L	4	Inc	2 (X.xx)	0 – 95
Uric Acid	Uric	umol/L	5	-	0 (XXX)	150 – 470
Alkaline Phosphatase, Bone Specific	BAP	mcg/L	6	-	1 (XXX.x)	0 – 20 (Mayo Clinic web site)
C-Reactive Protein	CRP	nmol/L	7	-	1 (XXX.x)	< 100 (Mayo Clinic web site)
Testosterone	TST	ng/dL	8	-	1 (XXXX.x)	300 - 1200
Coagulation						
International Normalized Ratio **[8]**	INR	ratio	1	Inc [*1,2,3*]	1 (X.x)	0.8 – 1.2 (healthy normals from Mayo Clinic web site)
Activated Partial Thromboplastin Time	aPTT	s	2	Inc [*1,2,3*]	0 (XX)	25 – 35
Prothrombin Time	PT	s	3		0 (XX)	11 – 13

All tables and listings must include the footnote: *See Statistical Analysis Plan Sections 13.3 and 13.4 for details regarding laboratory grading*

[1] Sort order (within panel) – N/A* are results that may be derived for analysis purposes and are reported only in listings (not tables).

[2] All CTCAE grading is based exclusively on quantitative laboratory results alone. Any associated clinical assessment by the investigator should be reported as an adverse event. When the CTCAE grade overlaps ranges based on clinical assessment, the higher grade is assigned.

[*1,2,3,4*] Indicates that not all grades are assigned in CTCAE – only those indicated are assigned by laboratory quantitative results

[3] Textbook normals to be used in absence of local normal ranges where reported units are obvious. Source is Merck Manual 2015 unless otherwise described

[4] For hemoglobin grading, in order to maintain the intention of CTCAE v4.03, the assumption is made that grading for increased levels are compared to ULN if baseline result is within normal range, or above baseline if baseline is above ULN.

[5] Serum calcium is corrected for albumin to assign CTCAE Grade; corrected calcium is derived as follows:

corrected-CA (mmol/L) = serum-CA (mmol/L) + 0.020 * (40 – albumin (g/L))

[6] To convert a BUN result in mg/dL to a Urea result in mmol/L, multiply the BUN result by 0.357. To convert a Urea result in mmol/L to a Urea result in mg/dL, multiply the mmol/L result by 6.

[7] Glucose results are assumed to be fasting for assignment of normal ranges and CTCAE grading.

[8] International Normalized Ratio assumes subjects are not on anticoagulant therapy.

13.4 NCI CTCAE v5.0 Laboratory Toxicity Grading

Lab Test (CTCAE Term)	Increase / Decrease	Grade 1	Grade 2	Grade 3	Grade 4
Hematology					
WBC (leukocytosis)	Increase	---	---	>100,000 /mm3	---
WBC (decreased)	Decrease	<LLN – 3000 /mm3 <LLN – 3.0 10^9/L	<3000 – 2000 /mm3 <3.0 – 2.0 10^9/L	<2000 – 1000 /mm3 <2.0 – 1.0 10^9/L	<1000 /mm3 <1.0 10^9/L
ANC (decreased)	Decrease	<LLN – 1500 /mm3 <LLN – 1.5 10^9/L	<1500 – 1000 /mm3 <1.5 – 1.0 10^9/L	<1000 – 500 /mm3 <1.0 – 0.5 10^9/L	<500 /mm3 <0.5 10^9/L
Lymphocytes (increased)	Increase	---	>4000 – 20,000 /mm3	>20,000 /mm3	---
Lymphocytes (decreased)	Decrease	<LLN – 800 /mm3 <LLN – 0.8 10^9/L	<800 – 500 /mm3 <0.8 – 0.5 10^9/L	<500 – 200 /mm3 <0.5 – 0.2 10^9/L	<200 /mm3 <0.2 10^9/L
Eosinophils (eosinophilia)	Increase	> ULN and > BL	---	---	---
Hemoglobin (anemia)	Decrease	<LLN – 10 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10 – 8 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8 g/dL <4.9 mmol/L <80 g/L	---
Hemoglobin (increased) [1]	Increase	>0 – 2 g/dL above ULN or above BL if BL is > ULN	>2 – 4 g/dL above ULN or above BL if BL is > ULN	>4 g/dL above ULN or above BL if BL is > ULN	---
Platelets (decreased)	Decrease	<LLN – 75,000 /mm3 <LLN – 75.0 10^9/L	<75,000 – 50,000 /mm3 <75.0 – 50.0 10^9/L	<50,000 – 25,000 /mm3 <50.0 – 25.0 10^9/L	<25,000 /mm3 <25.0 10^9/L
Coagulation					
APTT (prolonged)	Increase	>ULN – 1.5x ULN	>1.5 – 2.5x ULN	>2.5x ULN	---
INR (increased)	Increase	>1.2 – 1.5	>1.5 – 2.5	>2.5	---
Chemistry					
ALT (increased)	Increase	>ULN – 3.0x ULN if BL was normal 1.5 – 3.0x BL if BL was abnormal	>3.0 – 5.0x ULN if BL was normal >3.0 – 5.0x BL if BL was abnormal	>5.0 – 20.0x ULN if BL was normal >5 – 20.0x BL if BL was abnormal	>20.0x ULN if BL was normal >20.0x BL if BL was abnormal

Lab Test (CTCAE Term)	Increase / Decrease	Grade 1	Grade 2	Grade 3	Grade 4
AST (increased)	Increase	>ULN – 3.0x ULN if BL was normal 1.5 – 3.0x BL if BL was abnormal	>3.0 – 5.0x ULN if BL was normal >3.0 – 5.0x BL if BL was abnormal	>5.0 – 20.0x ULN if BL was normal >5 – 20.0x BL if BL was abnormal	>20x ULN if BL was normal >20.0x BL if BL was abnormal
ALK PHOS (increased)	Increase	>ULN – 2.5x ULN if BL was normal 2.0 – 2.5x BL if BL was abnormal	>2.5 – 5.0x ULN if BL was normal >2.5 – 5.0x BL if BL was abnormal	>5.0 – 20.0x ULN if BL was normal >5.0 – 20.0x BL if BL was abnormal	>20.0x ULN if BL was normal >20.0x BL if BL was abnormal
LDH (increased)	Increase	>ULN	---	---	---
Total Bilirubin (increased)	Increase	>ULN – 1.5x ULN if BL was normal >1.0 – 1.5x BL if BL was abnormal	>1.5 – 3.0x ULN if BL was normal >1.5 – 3.0x BL if BL was abnormal	>3.0 – 10.0x ULN if BL was normal >3.0 – 10.0x BL if BL was abnormal	>10x ULN if BL was normal >10.0x BL if BL was abnormal
Albumin (hypoalbuminemia)	Decrease	<LLN – 3.0 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	---
Creatinine (increased)	Increase	>ULN – 1.5x ULN	>1.5 – 3.0x ULN or >1.5 – 3.0x BL	>3.0 – 6.0x ULN or >3.0x BL – 6.0x ULN	>6.0x ULN
Glucose (hypoglycemia)	Decrease	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L
Lipase (increased)	Increase	>ULN – 1.5x ULN	>1.5 – 2.0x ULN	>2.0 – 5.0x ULN	>5.0x ULN
Amylase (increased)	Increase	>ULN – 1.5x ULN	>1.5 – 2.0x ULN	>2.0 – 5.0x ULN	>5.0x ULN
Corrected Calcium (hypercalcemia) [2]	Increase	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Corrected Calcium (hypocalcemia) [2]	Decrease	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Potassium (hyperkalemia)	Increase	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L

Lab Test (CTCAE Term)	Increase / Decrease	Grade 1	Grade 2	Grade 3	Grade 4
Potassium (hypokalemia)	Decrease	--	<LLN – 3.0 mmol/L	<3.0 – 2.5 mmol/L	<2.5 mmol/L
Magnesium (hypermagnesemia)	Increase	>ULN – 3 mg/dL >ULN – 1.23 mmol/L	---	>3 – 8 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L
Magnesium (hypomagnesemia)	Decrease	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L
Sodium (hypernatremia)	Increase	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L
Sodium (hyponatremia)	Decrease	<LLN – 130 mmol/L	---	120 - <130 mmol/L	<120 mmol/L
Uric Acid (increased)	Increase	---	---	> ULN	---

[1] For hemoglobin grading, in order to maintain the intention of CTCAE v4.03, the assumption is made that grading for increased levels are compared to ULN if baseline result is within normal range, or above baseline if baseline is above ULN.

[2] Serum calcium is corrected for albumin to assign CTCAE Grade; corrected calcium is derived as follows:

corrected-CA (mmol/L) = serum-CA (mmol/L) + 0.020 * (40 – albumin (g/L))