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Approval Task PPD Title: Consultant	Approved 24-Sep-2024 07:13:32 GMT+0000

Approval Task PPD Title: Director, Biostatistics	Approved 24-Sep-2024 07:20:18 GMT+0000

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STATISTICAL ANALYSIS PLAN

A multicentre, open-label, single-arm study to investigate the efficacy and safety of triptorelin pamoate 22.5 mg 6-month formulation in Chinese patients with locally advanced or metastatic prostate cancer

D-CN-52014-237

This statistical analysis plan is based on:
PROTOCOL VERSION AND DATE: 4.0 – 08 MARCH 2024

SAP Version	Date
Final Version 2.0	23 Sep 2024

APPROVAL PAGE

STUDY NUMBER:	D-CN-52014-237
PROTOCOL TITLE:	A multicentre, open-label, single-arm study to investigate the efficacy and safety of triptorelin pamoate 22.5 mg 6-month formulation in Chinese patients with locally advanced or metastatic prostate cancer
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The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan:

Name	Company	Function	Date	Signature
PPD	IPSEN	Statistics		eSignature
	IPSEN	Medical Director		eSignature
	Parexel	Statistics		eSignature

HISTORY OF CHANGES

Version Number	Date	Description/Rational for change
1.0	24 October 2022	New document
2.0	23 September 2024	Updated SAP per protocol version 4.
		Updated the listings for analysis set, demographic, baseline characteristics, medical history, non-drug therapies, medications, surgical procedures, testosterone level and PSA to present on all participants enrolled.
		Updated summary table with the number and percentage of participants per visit and the corresponding listing, summary table on duration of participant participation to present on all participants enrolled.
		Updated analysis set to Safety Set for summaries of medical history, non-drug therapies, medications and surgical procedures.
		Added treatment compliance summary.
		Plotted testosterone and PSA level data on semi-logarithmic scale.
		Added summary of exposure.
		Added TEAE definition for a continuous AE.
		Updated A6. CTCAE V5.0 Grading for Laboratory Values.
		Removed Summary of TEAE by treatment group, CTCAE grade, SOC and PT
		Removed the action of prohibited medication in section 5.7.2.1. The sample collected castrate levels of serum testosterone of participants with prohibited medication will be kept in statistical analysis.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AE	Adverse Event
ATC	Anatomic Therapeutic Class
AUC	Area Under the Plasma Concentration Time Curve
BLQ	Below Lower Limit of Quantification
C	Concomitant
CI	Confidence Interval
Cmax	Maximum Observed Concentration
eCRF	Electronic Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
gCV	Geometric Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
EoS	End of Study
EW	Early Withdrawal
FAS	Full Analysis Set
FDA	Food and Drug Administration
H	High
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
L	Low
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NC	Not Calculated
NCS	Not Clinically Significant
NMPA	National Medical Products Administration
NS	No Sample

ABBREVIATION	Wording Definition
NR	Not Reportable
P	Prior
PC	Prior and Concomitant
PD	Pharmacodynamics
PK	Pharmacokinetic
PN	Preferred Name
PPS	Per Protocol Set
PR	Time interval from the start of atrial depolarization to start of ventricular depolarization
PT	Preferred Term
QRS	Time interval for ventricular depolarization
QT	Time interval for ventricular depolarisation and repolarisation
QTc	Corrected QT interval
QTcF	Fridericia corrected QT internal
RR	Time between QRS complexes
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SEM	Standard Error Mean
SI	International System of Units
SOC	System Organic Class
SP	Service Provider
t_{cast}	Time to Castration
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
t_{max}	Time to Maximum Observed Concentration
WHODRUG	World Health Organisation Drug Dictionary

1 INTRODUCTION

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol D-CN-52014-237. It describes the rules and conventions to be used in the analysis and presentation of data, the data to be summarised and analysed, including specificities of the statistical analyses to be performed.

Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CSR.

The SAP is to be finalised before first participant enters the study. A separate shell will be provided for tables, figures and listings.

Any deviations from the SAP after database lock will be documented in the CSR (section 9.8 "Changes in the conduct of the study or planned analyses" as per International Conference on Harmonisation (ICH) E3).

This analysis plan does not cover pharmacokinetics (PK) and pharmacodynamics (PD) parameters determination and the relationship between triptorelin PK and testosterone PD analysis which will be described in a separate document.

2 PROTOCOL OVERVIEW

2.1 Study Objectives and Hypotheses

The primary objectives of the study are:

- To evaluate the efficacy of triptorelin pamoate 22.5 mg 6-month formulation in achieving castrate levels of testosterone
- To evaluate the efficacy of triptorelin pamoate 22.5 mg 6-month formulation in maintaining the castrate levels of serum testosterone

The secondary objectives are:

- To assess the safety profile including local tolerability of triptorelin pamoate 22.5 mg 6-month formulation
- To demonstrate the effect of triptorelin pamoate 22.5 mg 6-month formulation on prostate-specific antigen (PSA) response
- To assess the PK of triptorelin pamoate 22.5 mg 6-month formulation in a subset of 12 participants with rich PK sampling schedule
- To assess the PD of testosterone in a subset of 12 participants with rich PD sampling
- To assess the PK of triptorelin pamoate 22.5 mg 6-month formulation for all participants
- To assess the PD of testosterone for all participants

The exploratory objective is:

- To evaluate the PK/PD relationship between the PK of triptorelin pamoate 22.5 mg 6-month formulation and testosterone concentration versus time profiles

No statistical hypotheses are planned for this study.

2.2 Overall Study Design and Investigational Plan

This is a prospective, interventional, multicentre, open-label phase IIIb, single-arm study with a treatment period of 24 weeks for each participant. A total of 195 Chinese adult participants with locally advanced or metastatic prostate cancer will be enrolled in the study. All enrolled

participants will receive one injection of the 6-month formulation containing 22.5 mg triptorelin pamoate on Day 1.

This study will consist of a 4-week screening period, during which participants with advanced or metastatic prostate cancer will be screened for eligibility. On Day 1, eligible participants will receive a single open-label administration of the study intervention. Following treatment on Day 1, visits will occur on Day 2, Day 3, Day 5, Day 8, Day 15, Day 22 in a subset of 12 participants, and for all participants on Day 29, Day 57, Day 85, Day 113, Day 141 and Day 169.

The maximum duration of the study is approximately 30 months from screening to the last study visit. Participants who complete all scheduled visits will be considered to have completed the study. Participants who complete the study will have final procedures and assessments performed at the final visit (Day 169). Participants who withdraw from the study before the completion of the Day 169 evaluation period will have early discontinuation procedures and assessments performed at their final visit.

2.3 Sample Size Determination and Power

The sample size was estimated based on data from the previous Study DEB-TRI6M-301, 97.5% of participants achieving castration and 93% of participants maintaining castration from Week 8 to Week 24.

Sample size is calculated to fulfil the co-primary efficacy criteria of this study, which is to assess the proportion of participants achieving castrate levels of testosterone on Day 29 and the proportion of participants maintaining the castrate levels of serum testosterone from Week 8 to end of Week 24. A total of 195 participants with advanced prostate cancer will be enrolled to receive the triptorelin pamoate 22.5 mg 6-month formulation.

For an exact binomial test of a proportion with a two-sided nominal significance level of 0.05 and null proportion of 85%, a sample size of 165 participants has an exact power of 88.3% when the true proportion is 93% (of participants maintaining castration from Week 8 to Week 24). This sample size of 165 participants has a power >99.9% when the true proportion is 97.5% (of participants achieving castrate testosterone levels). Exact two-sided 95% confidence interval (CI) for a binomial proportion was computed by Statistical Analysis System (SAS) using the exact binomial distributions.

Assuming the dropout rate will be around 15%, a sample size of 195 participants in total is planned for this study.

2.4 Randomisation and Blinding

This is an open-label study. The study treatment assignment will be known to the participants, investigators, study centres, Sponsor, and any Service Provider (SP) affiliated with the study . Access to the data in the Electronic Data Capture (EDC) system is controlled and limited only to authorised personnel for specified data review.

2.5 Schedule of Assessments

Schedule of assessments is presented in section 1.3 from the protocol.

2.6 Change from Statistical Section of the Protocol

Protocol	SAP
Section 9.4.1.3 Demographic and Other Baseline Characteristics Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant disease (predosing AEs and ongoing medical history, prior medications and therapies, etc.) will be presented for the FAS, PP and safety sets.	Section 5.5 Medical history, non-drug therapies, medications and surgical procedures will be present for only Safety Set.

3 PLANNED ANALYSES

3.1 Data Monitoring

No independent Data Monitoring Committee (DMC) will be used in this study.

3.2 Interim Analysis / Primary Analysis

No interim analysis will be performed.

3.3 Final Analysis

Planned analyses will be done when all participants complete study and after database lock.

4 ANALYSIS SETS

Screened Set

The screened set will contain all participants screened (i.e. who signed the informed consent).

Full Analysis Set (FAS)

The FAS will contain all treated participants who complete the study or is a treatment failure.

Completing the study is defined as having serum testosterone measurement at baseline, Day 29 and Day 169. Treatment failure is defined as escaping castration (testosterone level ≥50 ng/dL or 1.735 nmol/L) at any assessments on and after Day 29 during the study, or premature discontinuation from the intervention period due to drug-related reasons (adverse event or death).

Per Protocol Set (PPS)

The PPS will contain all participants in the FAS who have no impacting major protocol deviations (i.e. that could potentially affect the primary efficacy endpoint outcome for the participant) as described in the protocol deviations document.

Safety Set

The safety set will contain all participants who receive the single dose of study intervention.

Rich PK Analysis Set (for non-compartmental analysis)

The rich PK analysis set will contain all participants in the PK/PD subset who receive one dose of study intervention, have no major protocol deviations affecting the PK variables, and who have a sufficient number of plasma concentrations to estimate the main PK parameters (maximum observed plasma drug concentration (C_{max}), time to maximum observed drug concentration (t_{max}) and area under the plasma concentration time curve (AUC)).

The criteria of major protocol deviations affecting the PK variables will be defined in the protocol deviation document. The process to review major protocol deviations potential impact on PK parameters will be ongoing and the final Rich PK Analysis Set will be determined during data review meeting.

Population PK Analysis Set

The population PK analysis set will contain all participants who received one dose of triptorelin and who have at least one triptorelin plasma concentration and no major protocol deviations affecting PK variables.

Rich PD Analysis Set

The rich PD analysis set will contain all participants in the PK/PD subset who have a sufficient number of PD (testosterone) measurements to estimate the main PD parameters (maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}) and time to castration (t_{cast})).

The efficacy analysis for the primary and secondary efficacy endpoints will be presented for the FAS and PPS population. The analysis of the safety data will be performed based on the safety set and analysis of PK and PD in the relevant PK/PD analysis set.

5 STATISTICAL METHODS/ANALYSES

The statistical analyses will be performed in accordance with ICH E9 guideline and guidelines presented in section 8.

SP will perform the statistical analysis of the efficacy, safety and PK/PD concentration data.

5.1 General Considerations

All statistical analyses will be performed using the Statistical Analysis System® software version 9.4 (or higher if available).

5.1.1 *Outputs Presentation*

5.1.1.1 Tables Header

Depending on the type of data, the summary tables will be presented as follows:

- For disposition, demographic and baseline data: by treatment group,
- For efficacy and safety data: by treatment group.

5.1.1.2 Presentation of Treatment Group

Tables, Figures and Listings (TFLs) will be displayed using the following treatment group label:

Triptorelin 6M

5.1.1.3 Presentation of Visits / Timepoints

Summaries by visit will be presented using visit number as collected in the Electronic Case Report Form (eCRF).

Visits in the TFLs will be presented as follows and in the following order:

Long Visit Name	Short Name
Screening	Scr
Baseline	Bsl
Day 1	D1
Day 2	D2
Day 3	D3
Day 5	D5
Day 8	D8
Day 15	D15
Day 22	D22
Week 4 Day 29	W4D29
Week 8 Day57	W8D57
Week 12 Day85	W12D85
Week 16 Day113	W16D113
Week 20 Day141	W20D141
End of Study/Early Withdrawal	EoS/EW

In the event a participant is enrolled, but does not receive study intervention, the participant will not remain in the study and EoS/EW assessment will not be performed.

5.1.2 *Descriptive Statistics*

All raw and derived variables will be listed and described using summary statistics. For categorical variables, summary statistics will be displayed using descriptive statistics by frequency count and percentages by category. The missing category will be presented if there is at least one missing category for at least one treatment group. Except otherwise specified, participants with missing data will be included in the calculation of percentages. For quantitative variables, summary statistics will be displayed using descriptive statistics by number of observations, mean, standard deviation (SD), median, minimum and maximum. Frequency and proportion of missing data will be displayed.

5.1.3 *Baseline Value*

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to first Investigational Medicinal Product (IMP) administration (including unscheduled assessments).

5.1.4 *Reference Start Date and Study Day*

Reference start date is defined as the day of the first IMP administration.

The day of the first IMP administration will be Day 1. Study day will be calculated as:

- The difference between the event date and the reference date plus one day, if the event is on or after the reference date.

- The difference between the event date and the reference date, if the date of event is prior to the reference date.

Study day will appear in any listings where an assessment date or event date appears.

In case of partial or missing event date, study day will appear missing while any associated durations will be presented based on the imputations described in appendix A2.

5.2 Randomisation, Disposition and Analysis Sets

Following disposition summaries and listings will be provided:

- Summary table with the number and percentages of screened and screen failure participants per centre on the screened set,
- Summary table with the number and percentage of participants screened, screen failed, reason for screen failures, treated, completer, withdrawn and reason for withdrawal, on the screened set,
- Summary table with the number and percentage of participants per visit for all participants enrolled,
- Summary table on duration of participant participation in the study. The definition of the duration of participant participation is from the date of initial consent to the date of end of study for all participants enrolled,
- Listing of dates of visit including study day (see section 5.1.4) for all participants enrolled,
- Listing of screen failure participants on the screened set,
- Listing of withdrawal participants for all enrolled participants who meet all eligibility criteria.
- Listing of participants not meeting at least one inclusion criteria and/or fulfilling at least one exclusion criteria on the screened set,
- Summary of the number and percentage of participants in each analysis set by centre, treatment group, based on all participants enrolled with reasons for exclusion from each analysis set,
- Listing including flag for each analysis set and reason for exclusion from each set on all participants enrolled.

5.3 Protocol Deviations

An exhaustive list of major protocol deviations that may occur during the course of the study and any action to be taken regarding exclusion of participants from the PPS is defined in Protocol Deviation Specification. Major protocol deviations will be determined before database lock of the study, finalised during the blind data review and documented in a separate document data review report.

Following protocol deviation summary and listing will be provided for all participants enrolled:

- Number and percentage of participants with major protocol deviations by deviation category (see DV section of Standard Study Data Tabulation Model (SDTM) user guide).
- A listing of major protocol deviations.
- A listing of all protocol deviations.

Visits impacted by the pandemic will also be summarized and listed.

5.4 Demography and Other baseline characteristics

All demographic and baseline characteristics summaries will be provided for the FAS, PPS and safety set. Listing will be provided on all participants enrolled.

Following summaries will be provided on:

- Demographic variables (refer to appendix A5 for EudraCT age categories),
- Other baseline characteristics (ECOG performance status, etc.),
- Disease characteristics (time since diagnosis [months], scan type [MRI, CT scan, Bone scan, other], scan location [prostate gland, pelvis, abdomen, chest, whole body, other], TNM stage of the disease, prior medication treatment for disease [Yes/No], Prior Radiotherapy for disease [Yes/No], Prior Surgical Procedures for disease [Yes/No]),

Time since diagnosis (months) = (Date of inform consent form - Date of histological diagnosis + 1) / 365.25*12. For participants who only have a year of the histological diagnosis date, the date of January 1 will be assumed. For participants who have both the year and month of the diagnosis date, the first date of diagnosis (01Mmmyyyy) will be assumed.

Listings will also be provided for all the summaries listed above.

5.5 Medical history, non-drug therapies, medications and surgical procedures

Medical and surgical history, non-drug therapies and surgical procedures will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) in effect within IPSEN at the time of database lock. Medications will be coded using the latest version of World Health Organization-Drug dictionary (WHODRUG) in effect within IPSEN at the time of database lock.

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the first IMP administration to allow classification as either Prior only, Prior and Concomitant, or Concomitant only:

Prior (P)	Start and stop dates prior to the date of the first IMP administration.
Prior and Concomitant (PC)	Start date before the date of the first IMP administration and stop date on or after the date of the first IMP administration.
Concomitant (C)	Start date on or after the date of first IMP administration.

Summary tables on prior medications/non-drug therapies/surgical procedures will include “P” only, summary tables on concomitant medications/non-drug therapies/surgical procedures will include “C” and “PC”.

See detailed rules in appendix A2 for classification of prior and concomitant medication/non-drug therapies, surgical procedures in case of partial/missing date.

Following summaries, presenting count and percentages of participants will be provided on the Safety Set:

- Significant medical and surgical history by primary system organ class (SOC) and preferred term (PT),
- Prior medications (P) for the study indication by ATC class and preferred Name (PN) (ATC level 2),
- Concomitant medications (PC, C) for the study indication by ATC class and preferred Name (ATC level 2),
- Prior surgical procedures (P) for the study indication by primary SOC and PT,

- Prior radiotherapies (P) for the study indication by primary SOC and PT,
- Prior medications (P) by ATC class and PN (ATC level 2),
- Concomitant medications (PC, C) by ATC class and PN (ATC level 2),
- Prior non-drug therapies (P) by primary SOC and PT,
- Concomitant non-drug therapies (PC, C) by primary SOC and PT,
- Concomitant surgical procedures (PC, C) by primary SOC and PT,

Listings will be provided for all the summaries listed above on all participants enrolled. These listings except medical and surgical history should include a flag indicating the category (P, PC, C) as described in the table above.

5.6 Compliance

Treatment compliance summary will be provided on the Safety Set, presenting count and percentages of participants who have administered all planned dose of Triptorelin.

5.7 Efficacy

5.7.1 *General Considerations*

The FAS and PPS will be used for efficacy analyses unless explicitly stated differently. Analysis on the FAS will be the primary analysis.

A listing of all efficacy data (raw and derived) will be provided (see listing detail conventions in Appendix A4). Descriptive statistics will be provided for all endpoints.

5.7.1.1 Significance Testing and Estimations

The statistical analysis of efficacy and safety is only descriptive therefore no formal statistical significance testing will be performed.

5.7.1.2 Handling of Dropouts and missing data

Diligent attempts will be made to limit the amount of missing data and to follow-up all treated participants to collect the primary and secondary efficacy endpoints for the statistical analysis.

Unless otherwise specified, missing data will not be imputed. But for analysis of the percentage of participants maintaining castration levels of testosterone, specific handling rules of missing data are described in section 5.7.2.1.

5.7.1.3 Statistical/analytical issues

Adjustments for Covariates

This is a single-arm study, and no statistical comparisons will be performed, so covariates adjustment is not required.

Interim Analyses and Data Monitoring

Please refer to section 3.

Multicentre Studies

This is a multicentre study conducted in China.

Multiple Comparisons/Multiplicity

No multiple testing will be performed in this study because this is a single-arm descriptive safety and efficacy study.

Active-Control Studies Intended to Show Equivalence (if applicable)

Not applicable.

5.7.2 *Analysis of Primary Efficacy Endpoint*

5.7.2.1 Endpoint, Treatment Effect and Estimand Definition

The co-primary endpoints of efficacy are

- To determine the percentage of participants achieving castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) on Day 29 ± 3 days (Week 4) and
- To determine the percentage of participants maintaining the castrate levels of serum testosterone (<50 ng/dL or 1.735 nmol/L) from Week 8 (Day 57 ± 3 days) to Week 24 (Day 169 ± 3 days).

Percentage of participants achieving castrate levels of serum testosterone on Day 29

The percentage of participants achieving castrate levels of serum testosterone on Day 29 will be obtained as the number of participants achieving castrate levels on Day 29, divided by the number of participants in the FAS. The formula is

$$\text{Percentage} = \frac{\text{Number of participants achieving castrate levels on Day 29}}{\text{Number of participants in the analysis set}} \times 100$$

Percentage of participants maintaining castrate levels from Week 8 to Week 24

Percentage of participants maintaining castrate levels of serum testosterone from Week 8 to Week 24 for the FAS will be calculated as the number of participants achieving castrate levels of serum testosterone at all visits from Week 8 to Week 24, divided by the number of assessable participants in the analysis set. The formula is

$$\text{Percentage} = \frac{\text{Number of participants maintaining castrate levels from Week 8 to Week 24}}{\text{Number of assessable participants in the analysis set}} \times 100$$

To derive the percentage of participants maintaining castration levels of testosterone, missing data between Week 8 and Week 24 will be handled as follows:

(a) In participants escaping castration at a certain visit (The escape event is defined as participant with a testosterone level >50 ng/dL), subsequent missing data is irrelevant; that is to say, participant will be treated as failure in that case.

(b) Participants maintaining castration up to a certain visit with missing data afterwards (drop-out due to non-drug-related reasons) will be excluded from the analysis.

(c) Participants maintaining castration up to a certain visit with missing data afterwards (drop-out due to drug-related reason) will be treated as having escaped castration (failure). Drug-related reason for drop-out is drug-related adverse event or death.

(d) Missing data at 1 or more visit(s) between two visits where castration levels are maintained will be handled as missing for that particular visit, and the participant will be considered to have maintained castration if all visits with available results are maintained.

To derive the percentage of participants maintaining castrate levels of testosterone, assessable participants are defined as the number of participants having values at all visits and all participants having missing data according to the criteria a), c) and d) mentioned above. Participants having missing data according to the criteria b) will be excluded from this calculation. Participants who discontinue before Week 8 will also be excluded from this calculation.

Because this is a descriptive post-approval commitment study, and the protocol was approved before National Medical Products Administration (NMPA) implementation of ICH E9 (R1), estimands will not be considered for this study.

5.7.2.2 Primary Analysis

The two primary endpoints will be tabulated with two-sided 95% CIs separately using the Clopper Pearson exact method for the FAS.

Castrate levels of serum testosterone will be summarized with descriptive statistics. Value below the lower limit of quantification (LLOQ) will be substituted by the LLOQ value for summary. Whether castrate level of serum testosterone is achieved (Yes/No) will also be summarized by visit.

Individual testosterone level data versus visit will be plotted by participant on a semi-logarithmic scale on the FAS with a dash line to indicate the testosterone limit of castration (50 ng/dL or 1.735 nmol/L) and a second dash line for the LLOQ. The arithmetic mean (±SD) and median testosterone levels versus visit will also be presented.

A testosterone level will be listed on all participants enrolled by participant and visit. All values below the limit of quantification will be listed as such.

5.7.2.3 Sensitivity Analysis

In addition, to further validate the analysis results of the primary endpoint, below sensitivity analyses will be conducted.

Sensitivity analysis 1: Analysis defined in section 5.7.2.2 (primary analyses for co-primary endpoints) will be repeated on the PPS.

Sensitivity analysis 2: Survival analysis to estimate the percentage of participants maintaining castrate levels from Week 8 to Week 24

Percentage of participants with castration levels (<50 ng/dL or 1.735 nmol/L) from Week 8 to Week 24, treated as a time-to-event endpoint, will be analysed by Kaplan-Meier method.

The event is defined as occurring in participants with a testosterone level ≥50 ng/dL or 1.735 nmol/L between Week 8 and Week 24 (escape event), and it will be presented as number of participants with escape event (event number), percentage of participants with escape event, achievement (<50 ng/dL or 1.735 nmol/L) rate by Week 8, Week 12, Week 16, Week 20, and Week 24 along with 95% CIs (calculated using the Greenwood's formula), minimum, maximum, median and 95% CI for median (calculated using Brookmeyer-Crowley method).

To accommodate drop-out and missing values the following censoring rules will be observed:

Table 5.1 Data Censoring Rules

Subject Discontinued	Week 8 - Week 24/Day of Discontinuation		To Be Handled As
	≥ 1 Missing Testosterone Value	Any Escape*	
Yes	No	No	Censored on day of last measurement
Yes	No	Yes	Event on day of first escape
Yes	Yes	No	Censored on day of last measurement before the first missing
Yes	Yes	Yes	Event on day of first escape
No	No	No	Censored on day of last measurement (date of EOS or Day 169)
No	No	Yes	Event on day of first escape
No	Yes	No	Censored on day of last measurement before the first missing
No	Yes	Yes	Event on day of first escape
No achievement by Week 8			Event on day of Week 8

*The escape (event) is defined as participant with castrate levels of serum testosterone ≥50 ng/dL or 1.735 nmol/L.

Below 3 percentages based on different populations are considered for calculation of percentage of participants maintaining castrate levels from Week 8 to Week 24:

Sensitivity analysis 3: All participants treated who complete the study or premature discontinuation from the intervention period due to any reasons will be included.

Sensitivity analysis 4: Participants in the FAS or PPS who do not discontinue from the treatment period prematurely due to drug-related reasons will be included.

Sensitivity analysis 5: Participants in the FAS or PPS without any missing data from Week 8 to Week 24 will be included.

5.7.2.4 Supplementary Analysis

Not applicable.

5.7.2.5 Subgroup Analysis

No subgroup analyses will be performed.

5.7.3 *Analysis of Key Secondary Efficacy Endpoints*

5.7.3.1 Endpoint, Treatment Effect and Estimand Definition

The secondary efficacy variable is the percent change in PSA from baseline (prior to injection) measured at Week 12 and Week 24. Percent change in PSA is defined as the value of difference between the PSA values at Week 12 and Week 24 and the baseline value divided by the baseline value.

$$\text{Percent change from baseline (\%)} = \left(\frac{\text{PSA value at Week 12 or Week 24} - \text{Baseline value}}{\text{Baseline value}}\right) \times 100$$

5.7.3.2 Main Secondary Analysis

PSA percent change from Baseline will be reported at each subsequent visit, using descriptive statistics on the FAS and PPS.

Observed value will also be summarized for the FAS. Descriptive statistics to be presented include number of available observations (n), mean, median, SD, minimum, maximum, standard error mean (SEM, calculated as SD divided by the square root of n), coefficient of variation (CV) and 95% CI for mean.

Individual PSA level data versus visit will be plotted by participant on a semi-logarithmic scale on the FAS. The arithmetic mean (±SD) PSA levels versus visit will also be provided.

All PSA data will be listed by participant and timepoint on all participants enrolled.

5.7.3.3 Subgroup Analysis

No subgroup analyses will be performed.

5.7.4 *Analysis of Other Secondary Efficacy Endpoints*

Not applicable.

5.7.5 *Analysis of Exploratory Endpoints*

An exploratory endpoint is defined in Protocol, but the analysis details will be described in a separate data analysis plan.

5.8 Safety

5.8.1 *General Consideration*

All safety summaries and analyses will be based upon the Safety Set. All safety data will be included in participant data listings (see listing detail conventions in Appendix A4). This is a single-arm study, and there will be no statistical comparison between the treatment groups for safety data.

Haematological and biochemical toxicities will be recorded and graded according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0 or higher, where available (refer to appendix A5 for grading using NCI-CTCAE 5.0). The NCI-CTCAE Grade 3 and 4 haematology and biochemistry variables by participant and by visit will be listed.

5.8.2 *Extent of Exposure*

Summary of the actual dose and duration of exposure will be provided on the Safety Set. Actual dose will be calculated as planned dose (22.5 mg) multiplied by (1 - percentage of residual in syringe). The definition of the duration of exposure is from first IMP administration to the date of end of study. Participant's exposure data will be listed on the Safety Set.

5.8.3 *Adverse Event*

All adverse events (AEs) recorded in the eCRF will be coded using the latest version of MedDRA dictionary in effect within IPSEN at the time of the database lock. AEs will be classified as Treatment-Emergent AEs (TEAEs) according to the rules below:

- Events with start date on or after the date of IMP administration and up to 24 weeks after date of first dose of treatment.
- Events whose severity (measured by National Cancer Institute – Common Toxicity Criteria (NCI-CTCAE) Version 5.0 grading) worsens on or after the date of IMP administration,

Refer to appendix ‘
Partial/Missing Date Convention’ for handling of partial date.

In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the most conservative case; i.e. treatment emergent.

In addition, if severity of an AE changes during the study, a separate AE will be recorded for each severity on the AE eCRF. The “first” and subsequent AEs will be identified based on the AE start date or the severity change date. If “first” AE record occurs before dosing, and subsequent AEs occur on or after dosing, subsequent AEs whose severity worsens compared with the severity of “first” AE record will be classified as TEAE. If first” AE record occurs on or after dosing, “first” AE record and subsequent AEs will be classified as TEAE.

The AE summaries include the following summaries:

- An overview table summarizing the
  - number and percentage of participants with at least one of the following AEs: any AE; any TEAE; any severe TEAE (CTCAE grade ≥ 3); treatment-related TEAE; TEAE leading to discontinuation from the study, Serious Adverse Event (SAE), treatment emergent SAE, treatment-related SAE, treatment emergent SAE leading to death, treatment-related SAE leading to death, treatment emergent SAE leading to discontinuation from the study, most frequent TEAEs (>5%), death,
  - corresponding number of events for each of the AE categories listed above
- A summary of the number and percentage of participants reporting a TEAE by treatment group, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by treatment group and PT,
- A summary of the number and percentage of participants reporting a TEAE by treatment group, maximum CTCAE grade, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by treatment group, maximum causality, SOC and PT,
- A summary of the number and percentage of participants reporting a treatment-related TEAE by treatment group, maximum CTCAE grade, SOC and PT,
- A summary of the number and percentage of participants reporting a most frequent TEAE (>5%) by treatment group and PT,
- A summary of the number and percentage of participants reporting a non-serious TEAE by treatment group, SOC and PT.

AEs summaries will be ordered in term of decreasing frequency for SOC and PT within SOC in the treatment group, and then alphabetically for SOC and PT within SOC if ties. AEs summaries by PT will be ordered in term of decreasing frequency of PT in the treatment group and then alphabetically for PT if ties.

AEs will be counted as follows:

- Participants with more than one AE within a particular SOC are counted only once for that SOC. Similarly, participants with more than one AE within a particular PT are counted only once for that PT;
- Participants reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case grade (grade order: 5>4>3>2>1>missing) will be used in the corresponding grade summaries;

- Participants reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case relationship to study medication (order: related > not related > missing) will be used in the corresponding relationship summaries;
- If the grade is missing for a TEAE, it will be considered as missing in the summary tables;
- Summary by grade will be presented;
- If the causality is missing for a TEAE, it will be considered related in the summary tables;
- The non-serious TEAEs table should include a specific row "any non-serious TEAE above 5%".

In addition, a listing with all AEs data will be listed by treatment group including non-TEAEs, Treatment-emergence status will be flagged in the listing.

Deaths, SAEs, and Other Significant Adverse Events

The following summaries will be provided:

- A summary of the number and percentage of participants reporting a SAE by treatment group, SOC and PT,
- A summary of the number and percentage of participants reporting a treatment emergent SAE by treatment group, SOC and PT,
- A summary of the number and percentage of participants reporting a treatment-related SAE by treatment group, SOC and PT,
- A summary of the number and percentage of participants reporting a SAE by treatment group, maximum CTCAE grade, SOC and PT,
- A summary of the number and percentage of participants reporting a SAE by treatment group, maximum causality, SOC and PT,
- A summary of the number and percentage of participants with TEAEs leading to discontinuation of study by treatment group, SOC and PT,
- A summary of the number and percentage of deaths (including SAEs with fatal outcome and deaths as PT) including primary reasons for death.

AEs of special interest is not applicable.

The following listings will be provided:

- A listing of all deaths that occurred during the study,
- A listing of all SAEs.
- A listing of TEAEs leading to discontinuation of study.

5.8.4 *Laboratory Data*

All laboratory data (Hematology and Clinical Chemistry) will be presented in the units of International System of Units (SI).

The following summaries will be provided:

- A summary of the actual and change from baseline in each laboratory parameter by treatment group and visit,
- A shift from baseline to each post-baseline timepoints of the number and percentage of participants experiencing low, normal or high values, by laboratory parameter,
- A shift from baseline to end of study according to Common Toxicity (CTC) grading system (Version 5.0 or higher),

For shift tables, the denominator should be the number of participants with both a baseline and a post-baseline assessment at a given timepoint.

In addition, the following listings are to be provided:

- A listing of all laboratory data. Out-of-reference-range values will be flagged as high (H) or low (L),
- A listing of all abnormal data.
- A listing of CTCAE grade 3 and higher values. All data for a laboratory parameter will be displayed for a participant who has any post-baseline value with CTCAE grade greater than or equal to 3 for the parameter.

5.8.5 *Vital Signs*

Blood pressure, temperature, respiratory rate and heart rate will be assessed. Any clinically significant vital signs will be recorded as AEs. The following summaries are to be provided:

- A summary of the actual and change from baseline in each vital sign parameter by treatment group and visit,
- A shift from baseline to post-dose in interpretation of clinical significance (normal, abnormal, not clinically significant [NCS], abnormal, clinically significant [CS]).

The following listing are to be provided:

- A listing of vital sign data.
- Listing of all abnormal data.

5.8.6 *Electrocardiogram (ECG)*

Results from the local lab units will be used.

The following quantitative ECG measurements will be taken during the study:

- heart rate (bpm),
- RR interval (msec),
- PR interval (msec),
- QRS interval (msec),
- QT interval (msec),

  Fridericia corrected QT (QTcF) interval (msec) = QT/$\sqrt[3]{RR}$);

An overall Investigator assessment of ECG will be provided as “normal”, “abnormal NCS” and “abnormal CS”. Any clinically significant abnormalities will be recorded as AEs.

The following summaries of ECG data may be appropriate:

- A summary of the actual and change from baseline in each ECG parameter by treatment group and visit,
- A shift from baseline (normal vs. abnormal NCS vs. abnormal CS) to each post-baseline visit.

The following listing are to be provided:

- A listing of ECG data.
- A listing of all abnormal data.

5.8.7 *Physical Examination*

The following summary and listings will be provided:

- A shift from baseline (normal vs abnormal NCS vs. abnormal CS) to each post-baseline visit by body system.
- A listing with any participants with at least one physical examination abnormality.

5.8.8 *Other*

Local tolerance will be assessed 2 hours (±15 minutes) after the single injection of 6-month formulation triptorelin, the injection site will be examined including but not limited to tenderness, erythema, swelling, haematoma, rash, pain, itching and induration. The presence of local tolerance will be listed and summarized for each symptom. The maximum length (mm) and width (mm) of presented symptom will also be summarized where applicable.

5.9 PK

5.9.1 *Triptorelin Plasma Concentrations*

Tables, listings and figures of triptorelin plasma concentrations will be generated by the SP for both the Rich PK Analysis Set and the Population PK Analysis Set.

Individual plasma concentrations of triptorelin will be listed and summarised by visit and time points using descriptive statistics for continuous variables including number of available observations (n), mean, median, SD, minimum, maximum, SEM, CV, geometric mean, geometric coefficient of variation (gCV) % (assuming log normally distributed data, and calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the SD of the log-transformed values) and 95% CI for mean.

Plasma concentrations should be displayed with the same precision than the LLOQ. In descriptive statistics, calculations derived from plasma concentrations (mean, minimum, maximum, median, SD etc.) should follow the same rule whereas CV% will only be displayed with one decimal digit.

Source data as reported from the laboratory will be used for calculation of concentration summary statistics. All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such. LLOQ will be presented as 'BLQ' in the listings and the LLOQ value presented as a footnote. Missing PK samples will be reported as no sample (NS) and/or not reportable (NR) and considered excluded from plasma concentration summary statistics. For summary tables, all BLQs will be considered as missing and will not be included in the summary statistics. The number of BLQs and non-BLQs at each scheduled time point will be reported. Summary Statistics will not be calculated if non-BLQ concentrations at a scheduled time point is less than 3 and if more than one third (1 out of every 3 values) are missing; in that case only minimum and maximum will be reported. Individual and mean triptorelin concentration time profiles, as well as spaghetti plots, will be generated.

5.9.2 *Triptorelin PK Analysis*

The PK analysis of triptorelin plasma concentrations for the rich PK Analysis Set will be performed by non-compartmental analysis (NCA). The NCA analysis will be described in a separate data analysis plan and reported in a standalone report. If warranted by the data population pharmacokinetics (PopPK) modelling will be performed on the Population PK Analysis Set using concentrations obtained from all participants in order to describe the pharmacokinetics of triptorelin 6-month formulation in the prostate cancer population. Population PK analysis will be described in a separate data analysis plan and presented in a standalone report.

5.10 Anti-drug Antibodies

Not applicable.

5.11 PD

5.11.1 *Testosterone Serum Concentrations*

Tables, listings and figures of testosterone serum concentrations will be generated by the SP for both the FAS and the Rich PD Analysis Set, following the same conditions described in 5.9.1 for triptorelin plasma concentrations.

5.11.2 *Testosterone PD Analysis*

The PD analyses of testosterone serum concentrations for the Rich PD Analyses Set will be performed by NCA. The NCA analysis will be described in a separate analysis plan and reported in a standalone report.

6 DATA HANDLING

6.1 Visit Window

Unless otherwise specified, no time window for visit/timepoints will be needed for analyses.

6.2 Unscheduled Visits, Retest, Withdrawal Visit,

All listings will include retests and unscheduled visits, while for the description by visit in the tables, only the scheduled visits according to the protocol will be described.

Unscheduled visit and retest measurements will be used to provide a measurement for a baseline data or endpoint value (e.g. worst value), if appropriate according to their definition. These measurements will also be used to determine abnormal laboratory, vital signs values or ECG.

If a value requires a retest (for laboratory values, vital signs and ECG) the closest non-missing reliable value to the scheduled visit will be used in the summary tables.

An assessment will be considered reliable if it is performed without any technical problem and if the result is within the range of likely values.

Participants who have withdrawn early from the study will have their last assessment entered at the end of study/early withdrawal visit in the eCRF. There is no remapping required for end of study/early withdrawal visit.

7 DERIVED DATA (IF APPLICABLE)

Not applicable.

8 REFERENCES

Reference to ICH regulatory guidelines:

- ICH E3: Structure and Content of Clinical Study Reports
- ICH E6 (R2): Good Clinical Practice
- ICH E9: Statistical Principles for Clinical Trials
- ICH E9 (R1) Addendum: Estimands and Sensitivity Analysis in Clinical Trials

Reference to European Medicines Agency (EMA) or point to consider guidelines:

- Adjustment for baseline covariates in clinical trials
- Choice of a non-inferiority margin

- Clinical trials in small populations
- Data monitoring committees
- Investigation of subgroups in confirmatory clinical trials
- Missing data in confirmatory clinical trials
- Application with Meta Analyses, One pivotal study
- Multiplicity issues in clinical trials

Switching between superiority and non-inferiority

Reference to Food and Drug Administration (FDA) guidelines:

- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics
- Multiple Endpoints in Clinical Trials

Reference to NMPA guidelines:

- Clinical trial data management and statistical analysis plan
- Submission of clinical trial data

Standard Ipsen SDTM user guide

Standard ADaMs user guide

Ipsen Global Style guide

Reference to statistical methods:

- Agresti A, Coull BA. Approximate is better than “exact” for interval estimation of binomial proportions. The American Statistician, 1998;52:119-26.
- Michael Laposata, MD PhD, SI unit conversion guide. The New England Journal of Medicine,1992

9 APPENDICES

A1. SAS Code

Sample code computing Clopper-Pearson 95%CI

"efficacy" sample data*

Participant ID	ACHPD (Achieve Testosterone at Day 29)	MAINPD (Maintain Testosterone from Week 8 to Week 24)
001	1	1
002	2	2
003	1	1
004	2	2
005	1	2
006	1	1
007	1	1

* This is just sample data for reference: 1 = Yes; 2 = No.

```
proc freq data=efficacy;
    table ACHPD / binomial;
    exact binomial;
run;
proc freq data=efficacy;
    table MAINPD / binomial;
    exact binomial;
run;
```

A2. Partial/Missing Date Convention

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / partial, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or the stop date indicates differently.
- Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the first IMP administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be "≥xx" according to the start and last visit dates).

Algorithm for Prior/ Concomitant

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the first IMP administration to allow classification as either Prior only, Prior and Concomitant, or Concomitant only.

In case of partial start and/or stop medication/ non-drug therapies/surgical procedures dates, imputation will be done to determine the classification:

- If a partial start date, the first day of the month will be imputed for missing day and January for missing month,
- If a partial stop date, the last day of the month will be imputed for missing days and December will be imputed for missing month.

In case incomplete start or stop date does not allow the classification, will be classified as concomitant.

Algorithm for TEAE

For deriving the TEAE flag the following process of temporary date imputation is done (for AE start date only assuming no AE end date are missing). The date imputation algorithm for incomplete adverse event start dates is described in Table 1. Classification of adverse event according to its treatment-emergent status is then done using the imputed date.

In the following table, all dates are presented using an YYYY-MM-DD format. As an example, suppose First IMP administration = 2002-08-11 and several AEs have incomplete start dates.

Table 1: Data imputation algorithm for AE start date

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day is missing			
YYYY-MM < YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-07-XX	2002-07-01
YYYY-MM = YYYY-MM of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-08-XX	Min (2002-08-11, AE end date)
YYYY-MM > YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-09-XX	2002-09-01
Day and month are missing			
YYYY < YYYY OF [First IMP admin.]	YYYY-01-01	2001-XX-XX	2001-01-01
YYYY = YYYY OF [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-11, AE end date)
YYYY > YYYY OF [First IMP admin.]	YYYY-01-01	2003-XX-XX	2003-01-01
Day, month, and year are missing			
XXXX-XX-XX	Min ([First IMP admin.], AE end date)		Min (2002-08-11, AE end date)

YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

If AE end date is partial, imputation could be done assuming the latest possible date (i.e. last day of month if day unknown, or 31st of December if day and month are unknown).

A3. Programming Convention for Outputs

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified.

The mean, median, and SD will be reported to one decimal place greater than the raw data recorded in the database. The minimum and maximum values will be reported with the same number of decimal places as the raw data recorded in the database. In general, the maximum number of decimal places reported should be four for any summary statistic.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentage will be calculated using n as denominator. The denominator n will be specified in a footnote for clarification if necessary. If sample sizes are small, the data displays will show the percentages, but in the CSR only frequency counts should be described.

P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.

Dates will be presented in the format [ddMmmyyyy] and times in the format [hh:mm].

A4. Listings Conventions

Any listings will contain at least the following data: participant identifier, age and gender. When dates are presented, the associated study days should be included. They should be sorted by treatment group then participant identifier. For multicentre studies, listings should be broken down by centre and treatment group.

A5. EudraCT Categories for Age

For EudraCT results summaries, in addition to quantitative descriptive statistics of age, demographic tables should include presentation of age using the following EudraCT categories (as applicable):

Adults (18-64 years)
From 65 to 84 years
85 years and over

A6. CTCAE V5.0 Grading for Laboratory Values

Grade is classified based on the numeric lab result criteria in CTCAE v5.0 grading. The clinical criteria or condition will not be used.

Analytic	CTCAE SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology							
Hemoglobin	Blood and lymphatic system disorders	Anemia	<LLN – 100 g/L	<100 - 80 g/L	<80 - 65 g/L	< 65 g/L	-
Hemoglobin	Investigations	Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN	Increase in >2 - 4 gm/dL above ULN	Increase in >4 gm/dL above ULN	-	-
Platelet count	Investigations	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10^9 /L	<75,000 -50,000/mm3; <75.0 - 50.0 x 10^9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10^9 /L	<25,000/mm3; <25.0 x 10^9 /L	-
White blood cell count (total)	Investigations	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10^9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10^9 /L	<1000/mm3; <1.0 x 10^9 /L	-
White blood cell count (total)	Blood and lymphatic system disorders	Leukocytosis	-	-	>100,000/mm3; >100 Giga /L	-	-
Neutrophils (Abs)	Investigations	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10^9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10^9 /L	<500/mm3; <0.5 x 10^9 /L	-
Lymphocytes	Investigations	Lymphocyte count decreased	<LLN -800/mm3; <LLN- 0.8 x 10^9/L	<800 - 500/mm3; <0.8 - 0.5 x 10^9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10^9 /L	<200/mm3; <0.2 x 10^9 /L	-
Lymphocytes	Investigations	Lymphocyte count increased	-	>4000 - 20,000/mm3; >4 - 20 Giga /L	>20,000/mm3; >20 Giga /L	-	-
Eosinophilia (Abs)	Blood and lymphatic system disorders	Eosinophilia	>ULN	-	-	-	-
Biochemistry							
Creatinine	Investigations	Creatinine increased	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	-
Glucose	Metabolism and nutrition disorders	Hyperglycemia	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L	-

Analytic	CTCAE SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Glucose	Metabolism and nutrition disorders	Hypoglycemia	<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	-
Total Bilirubin	Investigations	Blood bilirubin increased	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	-
Total Bilirubin	Hepatobiliary disorders	Sinusoidal obstruction syndrome	-	>34.2 - 85.5 umol/L	>85.5 umol/L	-	-
Alanine Aminotransferase	Investigations	Alanine aminotransferase increased	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Aspartate Aminotransferase	Investigations	Aspartate aminotransferase increased	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Alkaline Phosphatase	Investigations	Alkaline phosphatase increased	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-