CLCI699C2X01B

An open-label, multi-center, roll-over study to assess long term safety in patients with endogenous Cushing's syndrome who have completed a prior Novartis-sponsored osilodrostat(LCI699)study and are judged by the investigator to benefit from continued treatment with osilodrostat.

Statistical Analysis Plan

Version	3.2
Date	5 July 2023
Total Page Number	31
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Revision History

Date	Version	Summary of Changes
8 May 2018	1.0	First Version
13 January 2021	1.1	Change of sponsor – reformatting according with SOP 06BM13R02
16 July 2021	2.0	Implementation of protocol amendment 01 Introduction of interim analyses for safety
14 April 2023	3.0	Implementation of protocol amendment 02 Identification of the data from parent studies to complete baseline visit (W1D1) Deletion of output for section 10, 11 and 12
26 May 2023	3.1 (not issued)	Introduction calculation of CTCAE grading for lab parameters
26 June 2023	3.2	Update based on specific issues identified during interim analyses

Approval Page

Document Title: An open-label, multi-center, roll-over study to assess long term safety in patients with endogenous Cushing's syndrome who have completed a prior Novartis-sponsored osilodrostat (LCI699) study and are judged by the investigator to benefit from continued treatment with osilodrostat
Version 3.2

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Effective Date: 05 July 2023

Contents

1 LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

2 INTRODUCTION

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CLCI699C2X01B, an open label multi-center roll over study to assess long term safety in patients with endogenous Cushing's syndrome who have completed a prior Novartis –sponsored osilodrostat (LCI699) study and are judged by the investigator to benefit from the continued treatment.

2.1 CLINICAL OBJECTIVES

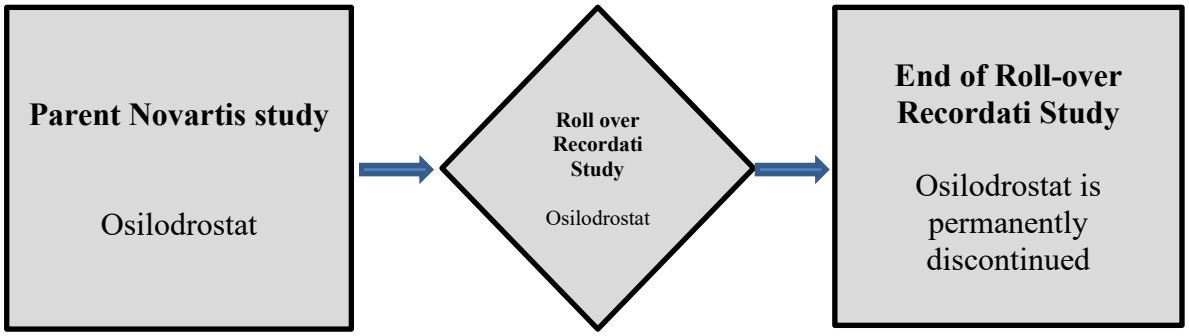
The purpose of the study is to evaluate the long-term safety.

2.2 STATISTICAL DESIGN / MODEL

This is a multi-center, open label phase IIb study to evaluate the long-term safety of osilodrostat in subjects receiving osilodrostat from Global Novartis-sponsored studies which has fulfilled its requirement for the primary objective, and who are judged by the parent study investigator as benefiting from continued treatment with osilodrostat.

There will be no screening period for this study. Eligible subjects can start their treatment with osilodrostat as soon as they are enrolled in the study. The first study visit will be scheduled at the time of the last study visit for the parent study. Subjects must return to the study center at least on a quarterly basis (every 12 weeks ± 2 weeks) for safety and clinical benefit assessments, and resupply of study medication. Drug dispensing and administration information and adverse events will be collected. The subject may return to the clinic at any given time as per standard of care or treating physician recommendation. All adverse events and serious adverse events, including pregnancy, will be collected throughout the study.
At every quarterly visit (every 12weeks ± 2 weeks), the Investigator is required to confirm that the subject continues to have clinical benefit and may continue receiving study treatment.

Figure 2-1 Study Design



2.3 INTERIM ANALYSES

In February 2021 the Pharmacovigilance Risk Assessment Committee (PRAC) requested the study sponsor to provide interim results of this roll-over study within the upcoming Periodic Safety Update Reports (PSURs). Therefore, regular interim analyses have been performed during the course of the study which will be aligned with the submission dates for the PSUR.
The final analysis will occur when all patients complete the study.
For the interim analyses, the following tables/listings have been provided (tables marked with "*" will be prepared only in case of request from the PRAC):

Tables

- Patient disposition (FAS)
- Demographics and baseline characteristics (FAS)
- Disease history (FAS)
- Duration of exposure to study drug during the overall study period excluding the parent study (Safety Set)
- Dose summary during the overall study period excluding the parent study (Safety Set)

- Dose summary during the overall study period including the parent study (Safety Set) *
- Overview of adverse events (Safety Set)
- Adverse events, regardless of study drug relationship, by system organ class (Safety Set)
- Adverse events, regardless of study drug relationship, in at least 10% patients (All Patients all grades) by preferred term (Safety Set)
- Adverse events, suspected to be study drug related, in at least 5% patients (All Patients all grades) by preferred term (Safety Set)
- Serious adverse events, regardless of study drug relationship, by preferred term (Safety Set)
- Serious adverse events, suspected to be study drug related, by preferred term (Safety Set)
- Adverse events of special interest, regardless of study drug relationship - Adrenal hormone precursor accumulation-related AEs (Safety Set)
- Adverse events of special interest, regardless of study drug relationship - Hypocortisolism-related AEs (Safety Set)
- Adverse events of special interest, regardless of study drug relationship - Arrhythmogenic potential AEs (Safety Set)
- Adverse events of special interest, regardless of study drug relationship - Pituitary tumour enlargement-related AEs (Safety Set)
- Adverse events of special interest, regardless of study drug relationship - QT prolongation AEs (Safety Set)

Listings

- Patient demographics (FAS)
- Subject disposition (FAS)
- Dose administration record (FAS)
- Adverse events (FAS)
- Serious adverse events (Safety set)
- Adverse events leading to study drug discontinuation (Safety set)
- Adrenal hormone precursor accumulation-related AEs (Safety Set)
- Hypocortisolism-related AEs (Safety Set)
- Arrhythmogenic potential AEs (Safety Set)
- Pituitary tumour enlargement-related AEs (Safety Set)
- QT prolongation AEs (Safety Set)
- Laboratory values by patient (biochemistry/hematology) (Safety Set) *
- Deaths (Safety Set)

Note that further outputs may be added as considered necessary.

2.3.1 Timing of interim analyses and design adaptations

Interim analyses have been performed by the CRO at the following time points:

- Q3 2021
- Q1 2022
- Q1 2023

Further time points might be added until the end of the study as needed.

2.4 STATISTICAL SOFTWARE

SAS version 9.4 or higher will be used in all analyses.

3 CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In this version the following changes have been added:

- To align the analysis plan with the amended Protocol version 02, the analysis of additional safety endpoints has been included.
- To comply with the PRAC request of adding to the PSUR of osilodrostat the available safety results of the study, corresponding interim analyses and relative times of analysis have been included.
- To identify data from parent studies to complete baseline visit (W1D1).

4 STATISTICAL METHODS

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

4.1 DATA ANALYSIS GENERAL INFORMATION

The statistical analysis of these data will be performed in accordance with the data analysis section, Section 10, of the study protocol which is available in [Appendix 16.1.1 of the CSR]. Important information is given in the following sections and details are provided, as applicable, in [Appendix 16.1.9 of the CSR].

In summary and analysis tables of continuous variables, standard descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum) will be presented. The minimum and maximum statistics will be presented in summary tables to the same number of significant figures as the original data. The mean, median, will be presented to one more significant figure than the original data, while SD will be presented to an additional significant figure. For derived variables one figure will be presented for mean, median, minimum, maximum and 25th and 75th percentiles (where requested) and two figures for SD.

In summary tables of categorical variables, the number of non-missing observations by category will be presented with percentages. All percentages will be presented to one decimal place.

4.1.1 General definitions

Baseline

For this study the baseline visit (W1D1) corresponds to the End of Treatment visit in the relative parent study.

The data for all assessments (except Obtain inform consent, Confirmation of Clinical Benefit from Study Treatment, and End of phase disposition) will be taken from the parent study.

Study Treatment

Study drug and investigational treatment refer to osilodrostat. Patients are to use the study treatment based on the parent protocol.

Date of first/last administration of study drug

The start date of study drug is defined as the first date when a non-zero dose of study drug was administered in the roll-over study and recorded on the Dosage Administration Record (DAR) eCRF.

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on DAR eCRF.

Date of first administration of study drug for total drug exposure

For the calculation of the total drug exposure the start date of study drug is defined as the first date when a non-zero dose of study drug was administered in the parent study and recorded on the Dosage Administration Record (DAR) eCRF.

4.2 PATIENT DISPOSITION, DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

4.2.1 Patient disposition

Patient disposition will be summarized overall using the Safety Set. The number (%) of treated patients included in the Safety Set will be presented. The number (%) of patients in the Safety Set who are still on treatment, who discontinued the study treatment and the reason for discontinuation will be presented overall.

The following summaries will be provided (with % based on the total number of Safety Set patients):

- Number (%) of patients who are still on-treatment at the time of data cut-off or final data base lock;
- Number (%) of patients who discontinued the study treatment;
- Number (%) of patients with primary reason for end of study treatment (based on patient status entered in the 'Treatment Disposition' page);
- Number (%) of patients who have entered the post-treatment follow-up safety evaluation (based on the 'Study Disposition' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'Study Dispostion' page);
- Number (%) of patients with primary reason for end of study (based on patient status entered in the 'Study Disposition' page);

Listings will be provided overall and by indication and formulation for disposition, informed consent, inclusion/exclusion criteria using the Safety Set.

4.2.2 Patient demographics and other baseline characteristics

Demographic information will be summarized and listed overall using the Safety Set. Demographic summary will include age and gender.

Categorical data (e.g., gender, age groups: <65 years, and ≥65 years) will be summarized by frequency counts and percentages. Continuous data (e.g., age) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum, 25th and 75th percentiles).

Demographic listing will include country, center, current patient ID, age and gender.

Medical history and ongoing medical conditions, including disease-related conditions and symptoms entered on (e) CRF will be summarized and listed overall. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

A listing of parent study history (parent study number, parent patient ID) will also be provided using the Safety Set.

4.3 TREATMENTS (STUDY TREATMENT, RESCUE MEDICATION, CONCOMITANT THERAPIES, COMPLIANCE)

4.3.1 Study treatment / compliance

Dose administration data will be summarized overall using the Safety Set.
Dose adjustments and reason for adjustments will be summarized (by frequency and percentage) by dose reduction or dose interruption (or both). Doses at the time of reduction or interruption will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum, 25th and 75th percentiles).

4.4 Measures for COVID-19 impact

Given the nature of the study, currently it is not planned any specific adjustments impacting the analysis unless the amount of the COVID-19 related protocol deviations would become relevant.

The types of protocol deviations that were expected due to the impact of COVID-19 included changes in procedures, missing visits, planned visits not done at sites and patient discontinuations due to COVID-19 situation or patients' health status.
The list of the protocol deviations due to the COVID-19 is reported in the Protocol Deviation Management Plan and will be summarized overall and listed.

5 VARIABLES AND ENDPOINTS

Objectives and related endpoints are described in Table 5-1 below altogether with the planned analysis of collected data.

Table 5-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To evaluate long term safety data, i.e., SAEs and AEs	Frequency and severity of AEs/SAEs	The assessment of safety will be based on the frequency and severity of adverse events (AEs) and serious adverse events (SAEs)
Secondary		
To evaluate clinical benefit as assessed by the investigator	Proportion of patients with clinical benefit as assessed by the investigator at scheduled visits	Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits
Other secondary		
To evaluate other safety data and tumor size	Lab parameters, vital signs, ECG, Tumor size and longest dimension	Shift tables vs Baseline and proportions of patients with notable abnormalities or grade 3 or 4

5.1 HANDLING OF MISSING DATA AND OUTLIERS

5.1.1 Study drug

Below mentioned imputation rules will be used in case of missing or partial end date of study drug.

Scenario 1

If the last date of study drug is after the cut-off date or is completely missing and there is no end of treatment eCRF page and no death date the patient should be considered to be on-going and use the cutoff date for the analysis as the last dosing date.

Scenario 2

If the last date of study drug is completely or partially missing and there is EITHER an end of treatment eCRF page OR a death date available, then imputed last dose date:

= 31DECYYYY, if only Year is available and Year < Year of min (EOT visit date, death date)

= Last day of the month, if both Year and Month are available and Year = Year of min

(EOT visit date, death date) and Month < the month of min (EOT visit date, death date)

= min (EOT visit date, death date), for all other cases

The imputed date will be compared with start date of study drug.

If the imputed date < start date of study drug, then last date of study drug is set to start date of study drug; otherwise, use the imputed date.

5.1.2 AE date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. Missing date for AE will be handled according to rules specified below. A partial date is simply an incomplete date e.g., DDOCT2001: the days are missing from this DDMMMYYYY date.

Partial AE start dates, if left partial, would ultimately mean the following:

It would not be possible to place the AE in time. Therefore, the treatment/dosage at the time of the event would be unknown. So, the event could not be reported/summarized appropriately – if at all.

Therefore, it is important to perform date imputation to ensure that as many data events are represented as correctly as possible. Of course, partial and/or missing dates should also be caught as edit checks and passed back to the investigator for resolution.

There **will be no** attempt to impute the following:

- **Missing** AE start dates
- AE start dates **missing the year**
- Partial/missing AE **end dates**

Table 5-2 AE/Treatment date abbreviations

	Day	**Month**	**Year**
Partial AE start date	<not used>	AEM	AEY
Treatment start date (TRTSTD)	<not used>	TRTM	TRTY

The following matrix Table 5-3 describes the possible combinations and their associated imputations. In the light grey boxes the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-3 AE partial date imputation algorithm

	AEM Missing	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY Missing	NC	NC	NC	NC
AEY < TRTY	Before TRTSTD (D)	Before TRTSTD (C)	Before TRTSTD (C)	Before TRTSTD (C)
AEY = TRTY	Uncertain (B)	Before TRTSTD (C)	Uncertain (B)	After TRTSTD (A)
AEY > TRTY	After TRTSTD (E)	After TRTSTD (A)	After TRTSTD (A)	After TRTSTD (A)

Table 5-4 AE/treatment date relationship and imputation legend

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC/Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

The following Table 5-5 gives a few examples.

Table 5-5 AE imputation example scenarios

Partial AE start date	Treatment start date	Relationship	Imputation calculation	Imputed date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

Any AEs with partial/missing dates will be displayed as such in the data listings.

Any AEs which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.2 DERIVATION RULES

5.2.1 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will be summarized separately.

5.2.2 Study day

Definitions will be applied for all situations:

- Study day for post-treatment event = event date – first dose date + 1
- Study day for pre-treatment event = first dose date - event date

The first day of study drug is study day 1.

If duration is to be reported in weeks, duration in days will be divided by 7, likewise if in months, then duration in days will be divided by 30.4375 and if in years, duration in days will be divided by 365.25.

5.3 DATA FROM PARENT STUDIES

Data referring to the disease history, as well as the height, were not collected in the study EDC but remained in the databases of the parent studies where the patients are coming from.

In addition, the data from the end of the treatment (or last visit) in the parent studies, will be extracted by the parent studies databases and transferred by the sponsor to the CRO. The date of the EOT visit from the parent study will be matched with the date of the baseline (W1D1) to guarantee the proper correspondence. The cases with a discrepancy exceeding one week between the two dates will be evaluated case by case.

For disease history they are the following ones:

- Time (months) to first study osilodrostat dose since diagnosis
- Classification at time of diagnosis
- Cushing's Disease Status
- Any previous surgery
- Any previous, non-LCI, treatments for Cushing's disease
- Any previous pituitary irradiation
- Baseline mean UFC.

For W1D1 visit the data to be transferred will regard the following topics:

- Vital signs (domain VS)
- ECG (domain EG)
- MRI (domains PR, FA)
- Laboratory (domain LB)

The data will be extracted as SAS datasets as close as possible to the domain structures reported in attachment 8.2.

6 ANALYSIS POPULATIONS

6.1 RELEVANT PROTOCOL DEVIATIONS

Protocol deviations will be categorized and tabulated overall and by indication and formulation into the following categories per ICH guidelines for CSR-reportable protocol deviations:

- Patient developed study/treatment withdrawal criteria during the study, but was not withdrawn
- Patient received the wrong treatment or incorrect dose
- Patient took an excluded concomitant medication
- Patient did not satisfy the entry criteria

Other important deviations may also be identified and summarized, as necessary, which may impact the scientific value of the trial.

All protocol deviations will be specified in the Study Specification Document (SSD).

All protocol deviations will be listed overall and by indication and formulation using Safety Set.

6.2 DEFINITION OF POPULATIONS FOR ANALYSIS

6.2.1 Full Analysis Set

6.2.2 For this study, the definition of FAS is the same as the Safety Set and in the tables the Safety Set will be indicated. Safety Set

The Safety Set includes all patients who received at least one dose of study medication (Osilodrostat) after enrolling into the roll-over protocol.

6.2.3 Subgroup of interest

Not Applicable

7 PLANNED ANALYSES

7.1 ANALYSIS OF THE PRIMARY OBJECTIVE

The primary objective is to evaluate long term safety as assessed by the occurrence of AEs / SAEs.

7.1.1 Primary endpoint

The assessment of safety will be based mainly on the frequency and severity of AEs, AESI and SAEs. See also Section 7.5.

7.1.2 Statistical hypothesis, model, and method of analysis

The primary endpoint will be summarized descriptively, overall no formal analysis will be performed. No hypothesis will be tested.

7.2 ANALYSIS OF SECONDARY EFFICACY OBJECTIVE(S)

The secondary objective of the study is to evaluate clinical benefit as assessed by the investigator.

7.2.1 Secondary endpoints

Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits. Clinical benefit will be summarized overall using the Safety Set.

7.3 EXTENT OF EXPOSURE

Definitions of duration of exposure, cumulative dose, average daily dose, as well as intermediate calculations, include:

Osilodrostat:

- Duration of exposure (weeks): (min (last date of rollover study drug, date of death, date of data cut-off) − first date of rollover study drug + 1)/7
- Cumulative dose (µg): total dose of study drug taken by a patient in the rollover study
- Number of dosing days (days): duration of exposure *7 − number of zero dose days
- Average daily dose (µg/day): cumulative dose (µg) / number of dosing days (days)

7.4 SAFETY ANALYSIS

Safety analyses will be performed on the Safety Set. The assessment of safety will be based mainly on the frequency of AEs, AESI and SAEs.

7.4.1 Adverse events (AEs)

Treatment emergent AEs are defined as those that started on or after the study medication, or those that started before study medication but worsened afterwards. AEs starting after 30 days after last dose of Osilodrostat treatment are not considered treatment emergent AEs.

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all safety data (including those from the post-treatment periods) will be listed and those collected during the post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity based on CTCAE grades (version 4.03 or higher), type of adverse event, relation to study treatment. The summary will include AEs regardless of study-drug relationship. The same analysis will be repeated for SAEs.

All treatment emergent AEs and SAEs will be listed. In this listing, the information on the relationship to study treatment will be included.

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology using the latest available MedDRA version at the time of the analyses and the information of MedDRA version will be specified in the footnote of relevant outputs.
The following selection of AEs will be listed and summarized separately using Safety Set. AEs will be summarized for all grades and for grade 3 or 4 side-by-side.

- AEs
- SAEs
- AEs leading to study drug discontinuation
- AEs requiring dose adjustment or interruption
- AEs requiring additional therapy
- Adverse events of special interest (AESI)

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 2% and on treatment-emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the Safety Set population.
If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- A single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- More than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.
The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Adverse events of special interest / grouping of AEs
The specific categories of AEs of special interest list for LCI699 are listed in attachment 8.1.

7.4.2 Laboratory parameters

Laboratory data summaries will include all assessments available for the lab parameters collected no later than 30 days of safety follow-up whichever is later after the last study treatment administration date using data from all sources. All laboratory assessments will be listed and those collected later than 30 days after the last study treatment date will be flagged in the listings.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. CTCAE version 5.0 will be applied and an extract of the tests that can be graded is reported in attachment 8.3.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

For laboratory tests where grades are not defined by CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE:

- Summary table for AEs of grades 3 or 4
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline

For laboratory tests where grades are not defined by CTCAE,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value

The following listings will be produced for the laboratory data (hematology, and biochemistry):

- Listing of all laboratory data with values flagged to show the corresponding CTC grades the classifications relative to the laboratory reference ranges
- Listing of notable laboratory abnormalities (i.e., CTC grade 3 or 4 laboratory toxicities).

7.4.3 Vital Signs

All vital signs data (body weight (kg) and systolic/diastolic blood pressure (mmHg)) will be listed by patient and visit/time. Shift tables based on notable values will be provided for vital signs. Change over time from baseline will be summarized.

Vital signs (sitting BP, HR & body weight) reporting of results will include:

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

Notable Values for vital signs will include:

- Systolic blood pressure [mmHg] at baseline: >=180 mmHg / <=90 mmHg –
- Diastolic blood pressure [mmHg] at baseline: >=105 mmHg / <=50 mmHg

Notably abnormal vital signs on treatment:

- Systolic blood pressure [mmHg] on treatment: >=180 mmHg with increase from baseline of >=20 mmHg / <=90 mmHg with decrease from baseline of >=20 mmHg;
- Diastolic blood pressure [mmHg] on treatment: >=105 mmHg with increase from baseline of >=15 mmHg/<=50 mmHg with decrease from baseline of >=15 mmHg;

7.4.4 Weight on treatment: Increase >=10% / Decrease >=5%ECG

ECG data will be summarized with:

- shift table baseline to worst on-treatment result for overall assessments
- number and percentage of patients with clinically notable abnormalities will be summarized
- listing of ECG evaluations for all patients with at least one abnormality.

A "notable abnormality" is defined as:

For PR are:

- > 200 ms post-baseline and ≤ 200 ms at baseline
- Increase > 25% compared to baseline to a post-baseline value > 200 ms

For QRS are:

- > 110 ms post-baseline and ≤ 110 ms at baseline
- Increase > 25% compared to baseline to a post-baseline value > 110 ms

For QT and QTcF are:

- > 450 ms at any post-baseline and ≤ 450 ms at baseline
- > 480 ms at any post-baseline and ≤ 480 ms at baseline
- > 500 ms at any post-baseline and ≤ 500 ms at baseline
- an increase from baseline > 30 ms at any post-baseline
- an increase from baseline > 60 ms at any post-baseline

For HR are:

- Increase >25% and HR >100 bpm
- Decrease >25% and HR <50 bpm

7.4.5 Tumor volume and longest dimension

For tumor volume evaluated by MRI scanning, descriptive summary of actual tumor volumes as well as its change from baseline will be provided at visits where evaluation is scheduled. For MRI images (or CT) that are not interpretable for tumor volume, the longest dimension (in mm) will be summarized instead. Due to evaluation schedule, this analysis will only be performed for the overall study period.

7.4.6 Deaths

Separate summaries for on-treatment death and all deaths *(including* on-treatment and post-treatment) will be produced by primary system organ class and preferred term overall using the Safety Set. On-treatment and all deaths will be listed overall, and post treatment deaths will be flagged.

8 ATTACHMENTS

8.1 LIST OF AES OF SPECIAL INTEREST

PT_NAME	PT_CODE	Safety Topic Of Interest
11-deoxycorticosterone increased	10081511	AESI Adrenal Hormone Precursor Accumulation-related AEs
11-deoxycortisol increased	10081510	AESI Adrenal Hormone Precursor Accumulation-related AEs
Acne	10000496	AESI Adrenal Hormone Precursor Accumulation-related AEs
Acquired apparent mineralocorticoid excess	10080230	AESI Adrenal Hormone Precursor Accumulation-related AEs
Androgenetic alopecia	10068168	AESI Adrenal Hormone Precursor Accumulation-related AEs
Androgens increased	10002265	AESI Adrenal Hormone Precursor Accumulation-related AEs
Blood potassium decreased	10005724	AESI Adrenal Hormone Precursor Accumulation-related AEs
Blood pressure diastolic increased	10005739	AESI Adrenal Hormone Precursor Accumulation-related AEs
Blood pressure increased	10005750	AESI Adrenal Hormone Precursor Accumulation-related AEs
Blood pressure systolic increased	10005760	AESI Adrenal Hormone Precursor Accumulation-related AEs
Blood sodium increased	10005803	AESI Adrenal Hormone Precursor Accumulation-related AEs
Blood testosterone free increased	10053785	AESI Adrenal Hormone Precursor Accumulation-related AEs
Blood testosterone increased	10005815	AESI Adrenal Hormone Precursor Accumulation-related AEs
Endocrine hypertension	10057615	AESI Adrenal Hormone Precursor Accumulation-related AEs
Generalised oedema	10018092	AESI Adrenal Hormone Precursor Accumulation-related AEs
Hair growth abnormal	10019044	AESI Adrenal Hormone Precursor Accumulation-related AEs
Hirsutism	10020112	AESI Adrenal Hormone Precursor Accumulation-related AEs
Hydroxycorticosteroids increased	10020534	AESI Adrenal Hormone Precursor Accumulation-related AEs
Hydroxycorticosteroids urine increased	10020539	AESI Adrenal Hormone Precursor Accumulation-related AEs
Hyperandrogenism	10065597	AESI Adrenal Hormone Precursor Accumulation-related AEs
Hypernatraemia	10020679	AESI Adrenal Hormone Precursor Accumulation-related AEs

PT_NAME	PT_CODE	Safety Topic Of Interest
Hypertension	10020772	AESI Adrenal Hormone Precursor Accumulation-related AEs
Hypertrichosis	10020864	AESI Adrenal Hormone Precursor Accumulation-related AEs
Hypokalaemia	10021015	AESI Adrenal Hormone Precursor Accumulation-related AEs
Hypokalaemic syndrome	10021017	AESI Adrenal Hormone Precursor Accumulation-related AEs
Localised oedema	10048961	AESI Adrenal Hormone Precursor Accumulation-related AEs
Oedema	10030095	AESI Adrenal Hormone Precursor Accumulation-related AEs
Oedema peripheral	10030124	AESI Adrenal Hormone Precursor Accumulation-related AEs
Cardiac arrest	10007515	AESI Arrhythmogenic potential AEs
Cardiac death	10049993	AESI Arrhythmogenic potential AEs
Cardiac fibrillation	10061592	AESI Arrhythmogenic potential AEs
Cardio-respiratory arrest	10007617	AESI Arrhythmogenic potential AEs
Loss of consciousness	10024855	AESI Arrhythmogenic potential AEs
Sudden cardiac death	10049418	AESI Arrhythmogenic potential AEs
Sudden death	10042434	AESI Arrhythmogenic potential AEs
Syncope	10042772	AESI Arrhythmogenic potential AEs
Torsade de pointes	10044066	AESI Arrhythmogenic potential AEs
Ventricular arrhythmia	10047281	AESI Arrhythmogenic potential AEs
Ventricular fibrillation	10047290	AESI Arrhythmogenic potential AEs
Ventricular flutter	10047294	AESI Arrhythmogenic potential AEs
Ventricular tachyarrhythmia	10065341	AESI Arrhythmogenic potential AEs
Ventricular tachycardia	10047302	AESI Arrhythmogenic potential AEs
Addison's disease	10001130	AESI Hypocortisolism related AEs
Adrenal insufficiency	10001367	AESI Hypocortisolism related AEs
Adrenal suppression	10001382	AESI Hypocortisolism related AEs
Adrenocortical insufficiency acute	10001389	AESI Hypocortisolism related AEs
Cortisol decreased	10011198	AESI Hypocortisolism related AEs
Cortisol free urine decreased	10011201	AESI Hypocortisolism related AEs
Glucocorticoid deficiency	10072079	AESI Hypocortisolism related AEs
Glucocorticoids decreased	10061466	AESI Hypocortisolism related AEs
Primary adrenal insufficiency	10052381	AESI Hypocortisolism related AEs
Secondary adrenocortical insufficiency	10039807	AESI Hypocortisolism related AEs
Steroid withdrawal syndrome	10042028	AESI Hypocortisolism related AEs
ACTH-producing pituitary tumour	10000613	AESI Pituitary tumor enlargement-related AEs
Cavernous sinus syndrome	10079769	AESI Pituitary tumor enlargement-related AEs
Chiasma syndrome	10067348	AESI Pituitary tumor enlargement-related AEs
Diplopia	10013036	AESI Pituitary tumor enlargement-related AEs
Extraocular muscle paresis	10015829	AESI Pituitary tumor enlargement-related AEs

PT_NAME	PT_CODE	Safety Topic Of Interest
III nerve disorder	10053644	AESI Pituitary tumor enlargement-related AEs
III nerve injury	10021281	AESI Pituitary tumor enlargement-related AEs
III nerve paralysis	10021283	AESI Pituitary tumor enlargement-related AEs
III nerve paresis	10054202	AESI Pituitary tumor enlargement-related AEs
IV nerve disorder	10065836	AESI Pituitary tumor enlargement-related AEs
IV nerve injury	10023108	AESI Pituitary tumor enlargement-related AEs
IV nerve paralysis	10023110	AESI Pituitary tumor enlargement-related AEs
IV nerve paresis	10054201	AESI Pituitary tumor enlargement-related AEs
Microvascular cranial nerve palsy	10079491	AESI Pituitary tumor enlargement-related AEs
Neoplasm progression	10061309	AESI Pituitary tumor enlargement-related AEs
Neoplasm recurrence	10061864	AESI Pituitary tumor enlargement-related AEs
Optic nerve compression	10076302	AESI Pituitary tumor enlargement-related AEs
Pituitary apoplexy	10056447	AESI Pituitary tumor enlargement-related AEs
Pituitary enlargement	10048675	AESI Pituitary tumor enlargement-related AEs
Pituitary haemorrhage	10049760	AESI Pituitary tumor enlargement-related AEs
Pituitary infarction	10035092	AESI Pituitary tumor enlargement-related AEs
Pituitary tumour	10035104	AESI Pituitary tumor enlargement-related AEs
Pituitary tumour benign	10061538	AESI Pituitary tumor enlargement-related AEs
Pituitary tumour recurrent	10057316	AESI Pituitary tumor enlargement-related AEs
Tumour compression	10068268	AESI Pituitary tumor enlargement-related AEs
Tumour invasion	10064390	AESI Pituitary tumor enlargement-related AEs
VI nerve disorder	10053646	AESI Pituitary tumor enlargement-related AEs
VI nerve injury	10047639	AESI Pituitary tumor enlargement-related AEs
VI nerve paralysis	10047641	AESI Pituitary tumor enlargement-related AEs
VI nerve paresis	10071044	AESI Pituitary tumor enlargement-related AEs
Visual field defect	10047555	AESI Pituitary tumor enlargement-related AEs
Electrocardiogram QT interval abnormal	10063748	AESI QT prolongation AEs
Electrocardiogram QT prolonged	10014387	AESI QT prolongation AEs
Long QT syndrome	10024803	AESI QT prolongation AEs

8.2 DATA FROM PARENT STUDIES

DATASET	VARIABLE	LENGTH	LABEL	ATTRIB
PR	STUDYID	200	Study Identifier	Character
PR	DOMAIN	200	Domain Abbreviation	Character
PR	USUBJID	200	Unique Subject Identifier	Character
PR	PRSEQ	8	Sequence Number	Numeric
PR	PRTRT	200	Reported Name of Procedure	Character
PR	PRCAT	200	Category	Character
PR	PRINDC	200	Indication	Character
PR	PRDOSE	8	Dose	Numeric
PR	PRDOSU	200	Dose Units	Character
PR	PRLOC	200	Location of Procedure	Character
PR	PRLAT	200	Laterality	Character
PR	VISITNUM	8	Visit Number	Numeric
PR	VISIT	200	Visit Name	Character
PR	VISITDY	8	Planned Study Day of Visit	Numeric
PR	EPOCH	200	Epoch	Character
PR	PRSTDTC	200	Start Date/Time of Procedure	Character
PR	PRENDTC	200	End Date/Time of Procedure	Character
PR	PRSTDY	8	Study Day of Start of Procedure	Numeric
PR	PRENDY	8	Study Day of End of Procedure	Numeric
FA	STUDYID	200	Study Identifier	Character
FA	DOMAIN	200	Domain Abbreviation	Character
FA	USUBJID	200	Unique Subject Identifier	Character
FA	FASEQ	8	Sequence Number	Numeric
FA	FATESTCD	200	Findings About Test Short Name	Character
FA	FATEST	200	Findings About Test Name	Character
FA	FAOBJ	200	Object of the Observation	Character
FA	FACAT	200	Category for Findings About	Character
FA	FAORRES	200	Result or Finding in Original Units	Character
FA	FAORRESU	200	Original Units	Character
FA	FASTRESC	200	Character Result/Finding in Std Format	Character
FA	FASTRESU	200	Standard Units	Character
FA	FASTAT	200	Completion Status	Character
FA	FAREASND	200	Reason Not Performed	Character
FA	FAMETHOD	200	Method of Test or Examination	Character
FA	VISITNUM	8	Visit Number	Numeric
FA	VISIT	200	Visit Name	Character

DATASET	VARIABLE	LENGTH	LABEL	ATTRIB
FA	VISITDY	8	Planned Study Day of Visit	Numeric
FA	EPOCH	200	Epoch	Character
FA	FADTC	200	Date/Time of Collection	Character
FA	FADY	8	Study Day of Collection	Numeric
LB	STUDYID	200	Study Identifier	Character
LB	DOMAIN	200	Domain Abbreviation	Character
LB	USUBJID	200	Unique Subject Identifier	Character
LB	LBSEQ	8	Sequence Number	Numeric
LB	LBREFID	200	Specimen ID	Character
LB	LBTESTCD	200	Lab Test or Examination Short Name	Character
LB	LBTEST	200	Lab Test or Examination Name	Character
LB	LBCAT	200	Category for Lab Test	Character
LB	LBORRES	200	Result or Finding in Original Units	Character
LB	LBORRESU	200	Original Units	Character
LB	LBORNRLO	200	Reference Range Lower Limit in Orig Unit	Character
LB	LBORNRHI	200	Reference Range Upper Limit in Orig Unit	Character
LB	LBSTRESC	200	Character Result/Finding in Std Format	Character
LB	LBSTRESN	8	Numeric Result/Finding in Standard Units	Numeric
LB	LBSTRESU	200	Standard Units	Character
LB	LBSTNRLO	8	Reference Range Lower Limit-Std Units	Numeric
LB	LBSTNRHI	8	Reference Range Upper Limit-Std Units	Numeric
LB	LBSTNRC	200	Reference Range for Char Rslt-Std Units	Character
LB	LBNRIND	200	Reference Range Indicator	Character
LB	LBSTAT	200	Completion Status	Character
LB	LBREASND	200	Reason Test Not Done	Character
LB	LBNAM	200	Vendor Name	Character
LB	LBSPEC	200	Specimen Type	Character
LB	LBSPCCND	200	Specimen Condition	Character
LB	LBMETHOD	200	Method of Test or Examination	Character
LB	LBBLFL	200	Baseline Flag	Character
LB	VISITNUM	8	Visit Number	Numeric
LB	VISIT	200	Visit Name	Character
LB	VISITDY	8	Planned Study Day of Visit	Numeric

DATASET	VARIABLE	LENGTH	LABEL	ATTRIB
LB	EPOCH	200	Epoch	Character
LB	LBDTC	200	Date/Time of Specimen Collection	Character
LB	LBENDTC	200	End Date/Time of Specimen Collection	Character
LB	LBDY	8	Study Day of Specimen Collection	Numeric
VS	STUDYID	200	Study Identifier	Character
VS	DOMAIN	200	Domain Abbreviation	Character
VS	USUBJID	200	Unique Subject Identifier	Character
VS	VSSEQ	8	Sequence Number	Numeric
VS	VSTESTCD	200	Vital Signs Test Short Name	Character
VS	VSTEST	200	Vital Signs Test Name	Character
VS	VSORRES	200	Result or Finding in Original Units	Character
VS	VSORRESU	200	Original Units	Character
VS	VSSTRESC	200	Character Result/Finding in Std Format	Character
VS	VSSTRESN	8	Numeric Result/Finding in Standard Units	Numeric
VS	VSSTRESU	200	Standard Units	Character
VS	VSBLFL	200	Baseline Flag	Character
VS	VISITNUM	8	Visit Number	Numeric
VS	VISIT	200	Visit Name	Character
VS	VISITDY	8	Planned Study Day of Visit	Numeric
VS	EPOCH	200	Epoch	Character
VS	VSDTC	200	Date/Time of Measurements	Character
VS	VSDY	8	Study Day of Vital Signs	Numeric
EG	STUDYID	200	Study Identifier	Character
EG	DOMAIN	200	Domain Abbreviation	Character
EG	USUBJID	200	Unique Subject Identifier	Character
EG	EGSEQ	8	Sequence Number	Numeric
EG	EGTESTCD	200	ECG Test or Examination Short Name	Character
EG	EGTEST	200	ECG Test or Examination Name	Character
EG	EGCAT	200	Category for ECG	Character
EG	EGORRES	200	Result or Finding in Original Units	Character
EG	EGORRESU	200	Original Units	Character
EG	EGSTRESC	200	Character Result/Finding in Std Format	Character
EG	EGSTRESN	8	Numeric Result/Finding in Standard Units	Numeric
EG	EGSTRESU	200	Standard Units	Character
EG	EGMETHOD	200	Method of ECG Test	Character
EG	EGBLFL	200	Baseline Flag	Character

DATASET	VARIABLE	LENGTH	LABEL	ATTRIB
EG	VISITNUM	8	Visit Number	Numeric
EG	VISIT	200	Visit Name	Character
EG	VISITDY	8	Planned Study Day of Visit	Numeric
EG	EPOCH	200	Epoch	Character
EG	EGDTC	200	Date/Time of ECG	Character
EG	EGDY	8	Study Day of ECG	Numeric

8.3 GRADING FOR LAB TESTS (V5.0)

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.					
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen.					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death

Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.					
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen.					
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.					
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.					
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.					
Hypomagnesemia	<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; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood.					
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death

Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.					
Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.					
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.					
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					
Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal.					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death

Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.
Navigational Note: -

Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-

Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.
Navigational Note: -

Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-

Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.
Navigational Note: -

Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-

Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.
Navigational Note: -

Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-

Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Navigational Note: -