COR-2017-OLE Statistical Analysis Plan (SAP) Cover Page

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Protocol COR-2017-OLE (OPTICS)

An Open-Label Extension Study of Levoketoconazole (2S,4R-ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Statistical Analysis Plan

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Approvals

The undersigned agree that all required reviews of this document are complete and approve this Statistical Analysis Plan as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

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Signature Date

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Signature Date

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Version History

Version #	Description of Changes	Version Date
1	Initial version	25 APR 2022
Amendment 1	1. Updated Section 5.1 to clarify that only two Baselines will be defined. Text throughout the SAP were updated to be consistent. 2. Updated Section 5.5 and 6.6.1 to clarify that the average of the Time to Midnight (in minutes) for the 2 LNSC samples will be calculated and used in analysis (where applicable). 3. Updated Section 6.1 to clarify that HbA1c will only be presented in conventional unit (%). 4. Updated Section 6.3 with more detailed description of the protocol deviation summary. 5. Removed the two hypertension/BP related categorical variables from Section 6.4.1. 6. Removed the reference to surgical history in Section 6.4.2. 7. Removed a statement in Section 6.6 regarding 95% confidence interval for the difference in the paired proportions. 8. Updated Section 6.6.1 to clarify that shift from baseline analysis includes shift from both the Original Baseline as well as the OLE Baseline. 9. Updated Section 6.7.2 to remove the by-visit categorical summary tables for laboratory tests, since the by-visit counts and percentages will also be presented in the by-visit shift tables. 10. Updated Section 6.7.3 to remove the by-visit categorical summary table for vital signs, since the by-visit counts and percentages will also be presented in the by-visit shift table. 11. Updated Section 6.7.7 to clarify that for TEAEs, only the TEAE overview and TEAE by SOC and PT tables will be produced for safety subgroups. 12. Updated Section 7 to document all the changes from planned analyses in the protocol. 13. There are also minor edits for accuracy.	28 JUN 2022
Amendment 2	1. Updated Section 4.2 to clarify that only subjects with major protocol deviations that could affect mUFC related efficacy endpoints would be excluded from PP population.	28 FEB 2023

Version #	Description of Changes	Version Date
	2. Updated Section 5.4 to clarify that the manual review of UFC collection date will only be conducted if necessary. 3. Updated Section 5.5 to clarify that if only 1 of the 2 scheduled LNSC samples are available or adequate, then that single sample will be used in the analysis instead of the mean. 4. Updated the nomenclature in Section 5.8, 6.6.2 and 7.5 for the two total severity scores for clinical signs and symptoms of Cushing's Syndrome: Total Signs Score and the Menstrual Abnormalities Total Score. 5. Updated Section 6.4.2, 6.4.3 and 6.7.1 to use the correct dictionary versions. 6. Updated the subgroup analysis of Age in Section 6.6.7 and 6.7.7 from "≤ median age vs. > median age" to "< median age vs. ≥ median age" (to achieve more balanced subgroups). 7. There are also minor edits for accuracy.	

Glossary of Abbreviations

Abbreviation	Term
aCRF	Annotated Case Report Form
ACTH	Adrenocorticotrophic Hormone
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BDI	Beck Depression Inventory
BID	Twice Daily
BMI	Body Mass Index
CD	Cushing's Disease
CO_2	Carbon Dioxide
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CS	Cushing's Syndrome
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eDISH	Evaluation of Drug-induced Serious Hepatotoxicity
FPG	Fasting Plasma Glucose
FPI	Fasting Plasma Insulin
GGT	Gamma-glutamyl Transferase
HbA1c	Hemoglobin A1c
HDL-C	High-Density Lipoprotein-Cholesterol
HOMA-%B	Homeostatic Model Assessment-Beta Cell Function
HOMA-IR	Homeostatic Model Assessment-Insulin Resistance
HR	Heart Rate
HRQoL	Health-related Quality of Life
hsCRP	High Sensitivity C-reactive Protein
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LDL-C	Low-Density Lipoprotein-Cholesterol
LFT	Liver Function Tests
LLN	Lower Limit of Normal
LNSC	Late Night Salivary Cortisol
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minimum
MRI	Magnetic Resonance Imaging

mUFC	Mean Urinary Free Cortisol
n	Number of subjects/observations
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OLE	Open-label Extension
PT	Preferred Term
QoL	Quality of Life
QTcB	Bazett corrected QT
QTcF	Fridericia corrected QT
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SI	International System of Units
SOC	System Organ Class
TFLs	Tables, Figures, and Listings
TSH	Thyroid-stimulating Hormone
UFC	Urinary Free Cortisol
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WHO	World Health Organization

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	26 March 2018	Original
Protocol Amendment 1	19 July 2018	Amendment # 1
Protocol Amendment 2	23 September 2019	Amendment # 2
Coronavirus Disease 2019 (COVID-19) Annex	17 April 2020	Version 1.0
Annotated Case Report Form (aCRF)	23 September 2021	Version 7

The planned statistical methodologies described in this SAP are in accordance with the principles outlined in the International Conference on Harmonization (ICH) E9.

2. Protocol Details

2.0 Study Objectives

The objective of this study is to assess long-term safety and efficacy durability of levoketoconazole as chronic treatment for endogenous Cushing's syndrome (CS).

2.1 Overall Study Design

This is a long-term, open-label extension (OLE) study of levoketoconazole in subjects with endogenous CS who have completed one or both parent studies or otherwise potentially qualify for this study, as defined in the entry criteria in the protocol.

For subjects entering directly from parent studies, the visit schedule for this OLE study is designed to overlap with those of the parent studies to ensure no break in drug supply for subjects as shown below in Table 1.

Table 1 Overlap with the Parent Study

Extension Study COR-2017-OLE Visit	Screening	Baseline
Can overlap with Parent Study COR-2012-01 (SONICS) visit: Parent Study COR-2017-01 (LOGICS) visit:	Month 9 (M9) Restoration Phase Visit 1 (RES1)	Month 12 (M12) Restoration Phase Visit 2 (RES2)

Subjects were to remain on their most recent therapeutic dose of levoketoconazole at entry. Certain subjects that were enrolled in the Titration and Maintenance Phase of Study COR-2017-01 when randomization was closed or subjects with a gap in treatment with levoketoconazole may require re-establishment or establishment of a Therapeutic Dose. As a result, dose titration may be required. Post-enrollment, levoketoconazole dose changes are permitted as needed. However, dose increases, which require prior Medical Monitor approval, are not to exceed 150 mg daily at one time nor be more frequent than every 2 weeks.

The study is comprised of Screening and Baseline Visits followed by scheduled visits every 3 months. In addition, Dose Adjustment/Safety Monitoring Visits are to be conducted in the event of a levoketoconazole dose increase.

Per Section 4.3 of the protocol, subject participation in the study was anticipated to continue for at least 3 years. The sponsor decided that effective 01 March 2022, subjects remaining in the study could continue participating through their Month 36 visit or 31 December 2022, whichever came first, with the following exception.

Subjects who already completed or were to have their Month 36 visit before 01 March 2022 will have their Month 39 visit after 01 March 2022 as their end-of-study visit.

The timings of study assessments are shown in Table 2 below.

Table 2 Time and Events Schedule

Assessments	Screening	Baseline	Every 3 Months (± 7 Days)	Every 6 Months (or 12 Months if indicated) (± 10 Days)[11, 13]	Dose Adjustment / Safety Monitoring Visit[12,14]	Final Study Visit	Safety Follow-Up Call[15]
COR-2012-01 Visit Alignment[1,2]	M9	M12					
COR-2017-01 Visit Alignment[1,2]	RES1	RES2					
Expanded Access Program	Screening & Baseline should occur within 3-4 weeks of each other						
Informed Consent	X						
Eligibility Check	X	X					
Prior/concomitant Medications	X[3]	X[3]	X		X	X	
Pregnancy Test (urine βhCG), females	X[3]	X[3]	X		X	X	
Adverse Events	X[3]	X[3]	X		X	X	X
ECG (central read) [4]	X[3]	X[3]	X		X	X	
Vital Signs (temperature, BP, heart rate)[5]		X[3]	X		X	X	
Body weight/height/BMI (derived)		X[3]	X		X	X	
Physical Examination		X[3]		X		X	
CS Signs and Symptoms		X[3]		X		X	
Safety Laboratory Tests (including hematology, chemistry, LFTs, urine dipstick)[6]	X[3]	X[3]	X		X	X	
Serum Cortisol (am)		X[3]	X		X	X	
Late Night Salivary Cortisol (2 nights)		X[3, 7]	X		X	X	
ACTH		X[3]		X	X	X	
24-h UFC (2-3 collections)[8]		X[3]		X	X	X	
CS Biomarkers FBG, fasting insulin, HOMA-IR, HbA1C, total cholesterol, HDL-C, LDL-C, hsCRP		X[9]		X		X	
Pituitary MRI (pituitary tumor patients only)		(X)[10]		X[10, 13]		X	

Assessments	Screening	Baseline	Every 3 Months (± 7 Days)	Every 6 Months (or 12 Months if indicated) (± 10 Days)[11, 13]	Dose Adjustment / Safety Monitoring Visit[12,14]	Final Study Visit	Safety Follow-Up Call[15]
Cushing QoL questionnaire		X[3]		X		X	
BDI-II instrument		X[3]		X		X	
Subject Diary	X[16]	X	X		X		
Dispense drug		X	X				
Administer drug and/or drug accountability		X	X		X	X	

1 Procedures performed during the listed parent study visits should not be repeated for the OLE. Rather, the OLE will make use of data already captured for these parent study visits. The informed consent and eligibility check may occur on a date that is different from the parent study clinic visit, if this is completed > 1 month prior to the anticipated date for the end of treatment on the parent study.
2 This Time and Events Schedule does not account for additional tests that need to be collected as part of COR-2012-01 or COR-2017-01, for subjects whose parent study visits align with OLE Screening and/or Baseline. Refer to parent study's respective Time and Events Schedule.
3 Assessment overlaps with parent study.
4 12-lead ECGs should be obtained prior to first dose of drug as a Baseline and every 3 months (or after dose increases) after enrollment. ECGs should be obtained within approximately 1 to 2 hours after drug administration and after the subject has rested in a supine position for at least 5 minutes after the subject has not eaten for at least 2 hours. NOTE: For subjects entering from Study COR-2012-01 the Spaulding device previously used in the parent study is not planned for use in this study. However, it is acceptable to use the prior device for the OLE Screening and/or Baseline Visit.
5 BP and heart rate will be done in triplicate.
6 If urine dipstick is positive for protein and ketones, send urinalysis to the lab for assessment.
7 Ensure that 2 collections are done immediately prior to Baseline and results are available
8 Three collections of 24-hr urinary free cortisol (UFC) will occur at every visit marked in the Time and Events Schedule, except for if a subject's OLE Baseline Visit overlaps with M12 (as part of COR-2012-01), then 2 collections will be collected.
9 hsCRP and fasting insulin are not assessed in COR-2012-01 but are assessed in this study, in addition to performing the parent study's assessments (including CRP) if M12 aligns with OLE Baseline, Investigators would also conduct a hsCRP and fasting insulin assessment at Baseline.
10 If not done within 6 months of the OLE Baseline Visit.
11 Assessments listed here are in addition to those done every 3 months.
12 Dose Adjustment/Safety Monitoring Visits will be conducted in accordance with the requirements specified in Section 6.1.6 of the protocol.
13 Annually (the scheduled interval between MRIs should be once every 12 (± 2) months).
14 Liver Function tests (AST, ALT, GGT, AP, LDH, total and direct bilirubin) to be done biweekly for 1 month (twice in total) unless total daily dose is greater than 600 mg, then weekly (4 times for 1 month), 12-lead ECG (to check for evidence of QTc prolongation) to be conducted 1 to 2 hours after dosing at the new (higher) dose and again after 1 month and cortisol monitoring (e.g. UFCs, Serum Cortisol, Salivary Cortisol) biweekly for 1 month (twice in total).
15 Safety Follow-Up Call to be conducted 1 week following the Final Study Visit
16 To be dispensed for subjects entering from Expanded Access Program or for those that had a gap in treatment with levoketoconazole

2.2 Sample Size and Power

Given that this is a single-arm OLE study with exploratory efficacy endpoints only, there is no formal hypothesis testing, and the sample size to be enrolled is not pre-determined.

3. Study Endpoints

3.0 Exploratory Efficacy Endpoints

The following efficacy endpoints will be assessed. All efficacy endpoints are considered exploratory. Refer to Section 5.1 for the definitions of Baseline.

• Proportions of subjects with mean urinary free cortisol (mUFC): 1) Less than or equal to the upper limit of normal (ULN) of the reference range; 2) Above the ULN to 1.5X the ULN; and 3) Above 1.5X the ULN;

• Changes from Baseline in mUFC and late night salivary cortisol (LNSC);

• Proportion of subjects with LNSC above the ULN of the reference range;

• Changes from Baseline in Clinical Signs and Symptoms of CS, health-related quality of life (QoL), and symptoms of depression;

• Changes from Baseline in biomarkers of CS comorbidities (fasting blood glucose [FBG], fasting insulin, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c], blood pressure, total cholesterol, high-density lipoprotein-cholesterol [HDL-C], low-density lipoprotein-cholesterol [LDL-C], high-sensitivity C-reactive protein [hsCRP]);

• Frequency of usage and changes from Baseline in frequency of usage of anti-diabetic, anti-cholesterol, and anti-hypertensive therapies;

• Compliance (adherence) and persistence with therapy per tablet counts.

3.1 Safety Endpoints

Safety will be assessed by incidence and severity of all Adverse Events (AEs), Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) as well as by physical examinations, safety laboratory panels (including Adrenocorticotropic Hormone [ACTH], liver function tests [LFTs], blood chemistry, hematology), electrocardiograms (ECGs) (to include assessment of the QTc interval), vital signs and pituitary Magnetic Resonance Imaging (MRI) for subjects with history of a pituitary tumor.

4. Analysis Populations

4.1 Intent-to-treat (ITT) Population

The ITT population will include all subjects who provide informed consent and receive at least one dose of levoketoconazole. This population will be used for the analyses of safety and efficacy.

4.2 Per-protocol (PP) Population

The PP population will include all subjects in the ITT population who have no major protocol deviations during the study that could affect mUFC related efficacy endpoints. This population will be used for selected efficacy analyses if the PP population is < 90% of the ITT population.

Additional subsets of the ITT and/or PP populations (for example, ITT population with diagnosis of Cushing's Disease [CD]) may also be used for efficacy analyses as applicable.

5. Data Handling

5.1 Baseline, First Dose Date, and Last Dose Date

For the purposes of analyzing changes or shifts from Baseline, whether for safety or efficacy evaluations, two Baselines will be used: the OLE study baseline and the original (i.e., parent) study baseline, as applicable. These Baselines will be designated as OLE Baseline and Original Baseline, and defined as follows:

OLE Baseline

The OLE Baseline value is the pre-dose value collected on the Baseline visit Case Report Form (CRF).

Original Baseline

For subjects who completed SONICS, the Original Baseline value is the original study baseline value in SONICS. For subjects who did not participate in SONICS, the Original Baseline value is the original study baseline value in LOGICS.

The change from baseline analysis will, in general, include changes from Original and OLE Baselines.

5.2 Study Day

Study day is calculated based on the date of first levoketoconazole dose in this study:

- If the date of assessment is before the date of first dose, then Study Day = Date of assessment minus First levoketoconazole dose date;
- If the date of assessment is on or after the first dose date, then Study Day = Date of assessment minus First levoketoconazole dose date plus 1 day;

Day 1 is defined as the day of first dose of levoketoconazole in this study. The day prior to Day 1 is Day -1.

5.3 Time Points and Visit Windows

Table 3 below presents the visit windows that will be used for the by-visit analysis of efficacy and safety. It also presents the visit window that will be used for the End of Study time point analysis of efficacy and safety.

Table 3 Visit Windows for by-visit Analysis of Efficacy and Safety

Nominal Visit/Time Point	Target Study Day (range)	Study Day Analysis Visit Window Range
M3	91	Days 2 to 137
M6	183	Days 138 to 229

M9	274	Days 230 to 320
M12	365	Days 321 to 411
M15	457	Days 412 to 503
M18	548	Days 504 to 594
M21	639	Days 595 to 685
M24	731	Days 686 to 777
M27	822	Days 778 to 868
M30	913	Days 869 to 959
M33	1004	Days 960 to 1050
M36	1096	Days 1051 to 1142
End of Study	No specific target day (range) specified	No specific study day analysis visit window range specified, so long as it is during the study. The last non-missing post-baseline result in the study for a subject will be used for the End of Study time point.

Multiple visits within the same window will be dealt with as follows:

- If both scheduled and unscheduled visits fall within the same visit window, then the scheduled visit will be used for analysis, except for by-visit safety endpoints (e.g., laboratory evaluations) when they are analyzed with respect to the reference ranges (e.g., shift tables) or prespecified thresholds; the worst results among all scheduled and unscheduled visits within the same visit window will then be used instead. For vital signs (specifically blood pressure and heart rate) and ECG intervals (specifically QT, QTcF, QTcB, PR, and QRS), the worst result for a subject in a visit window is defined as the maximum value for that subject in that visit window. For the safety laboratory tests, the worst result for a subject in a visit window can be the maximum or minimum value, depending on the laboratory test. Refer to Appendix 1 for details on the identification of the worst results for safety laboratory tests.
- If multiple scheduled visits occur within a single visit window, then the visit closest to the target day of the visit window will be used in the analysis. If there is a tie, then the later scheduled visit will be used in the analysis.
- If multiple unscheduled visits occur within a single visit window (with no scheduled visit within the window), then the unscheduled visit closest to the target day of the visit window will be used in the analysis. If there is a tie, then the later unscheduled visit will be used in the analysis.

5.4 Urinary Free Cortisol – Determination of Adequacy and Calculation of Mean

Three 24-hour urine collections for UFC are scheduled (usually 7-14 days prior) at every visit indicated in Table 2, except when a subject's OLE Baseline Visit overlaps with M12 (as part of SONICS), when two 24-hour collections are scheduled.

For the analyses of all UFC-related endpoints, only UFC values from adequate urine collections will be included. The urine creatinine excretion rate will be measured from the 24-hour urine samples as a marker of the adequacy of the urine collections. For analysis purposes, a urine sample for UFC is considered to be adequate if its corresponding urine creatinine excretion is ≥ 4.5 mg/kg/day for females and ≥ 6.2 mg/kg/day for males. The thresholds of 4.5 mg/kg/day for females and 6.2 mg/kg/day for males were based on the mean minus (2 times standard error) of all urine creatinine excretion values in the SONICS study by sex, which meant that approximately 2.5% of the urine creatinine excretion values from SONICS were < 4.5 mg/kg/day for females and < 6.2 mg/kg/day for males. It is anticipated that this study will have about the same overall means by sex and, therefore, using these thresholds will result in excluding about 2.5% of all samples from analyses. These thresholds were the same ones applied for analysis purposes in the LOGICS study. These thresholds are different from the criteria for adequacy that are defined in Section 6.2.5.1 of the protocol, which were used by sites for purposes of determining whether 24-hour urine samples were acceptable.

At every visit, the corresponding mUFC will be calculated using only UFC values from adequate 24-hour urine collections. A minimum of two adequate samples are required for calculation of mUFC. If only one adequate sample is available, then mUFC will be set to missing.

5.5 Late Night Salivary Cortisol – Calculation of Means

LNSC samples from 2 nights will be collected between 11 PM and midnight at each visit indicated in Table 2. For mean LNSC analyses, only adequate samples, defined as those collected between 10 PM and midnight (i.e., a 1-hour allowance earlier), and with collection dates within the analysis window for that visit will be included in the calculation. If only one adequate sample is available, then the single sample will substitute for the mean. Collection time to midnight (in minutes) will also be averaged for the mean LNSC using the same criteria.

5.6 Blood Pressure and Heart Rate – Calculation of Means

Blood pressure and heart rate are measured in triplicate at each visit. The mean of the measurements will be used as the result for each visit, to be calculated only if

there are at least 2 measurements. If there is only one measurement, then mean will be set to missing.

5.7 Cushing's Syndrome Quality of Life and Beck Depression Inventory (BDI)-II – Calculation of Total Scores and Subscale Scores

The CS QoL questionnaire is a general questionnaire with 12 items that assess subject health-related quality of life. Answers to QoL are based on the Likert scale with five response categories, rated on a scale of 1-5, where '1' corresponds to 'Always' or 'Very much' and '5' to 'Never' or 'Not at all'. The lower the score, the lower the health-related quality of life (HRQoL). The total score for QoL is the sum of all the item responses and can range from 12 (worst score) to 60 points (best score). A standardized total score on a scale from 0 (worst HRQoL) to 100 (best HRQoL) will be calculated with the following formula:

$$\text{Standardized total score} = \frac{TotalScore - \min}{\max - \min} \times 100$$

where 'min' is the minimum (min=12 if all 12 item responses are non-missing), and 'max' is the maximum possible score (max=60 if all 12 item responses are non-missing).

If more than 3 items have a missing response, then the total score will be considered missing for that visit. The standardized total score can be calculated (as above) if the number of unanswered items does not exceed 3 (25% of the questions). In this case, the standardized total score will have min = the number of item responses that are non-missing and max = 5 x the number of item responses that are non-missing.

In addition, CS QoL results will be analyzed using a 2-subscale scoring solution (Tiemensma 2016), where questions 1, 3, and 4 are grouped as the Physical Problems subscale (calculable when there are no missing items), and the remaining 9 questions are grouped as the Psychosocial Issues subscale (calculable when two or fewer items are missing). Within each subscale, the same standardization as mentioned above will be used on the subscales, keeping both subscales and the total score on the same metric.

The BDI-II inventory comprises 21 questions, each with a score from 0 to 3. Scores for each question are summed to create a total score. A total score between 0 and 13 indicates minimal, 14 to 19 mild, 20 to 28 moderate, and 29 to 63 severe depression. Scoring information for the 21 questions is detailed in Appendix M of the protocol. If one question has a missing score, then the missing score will be imputed as the average of the non-missing scores for that question in the ITT population. If more than 25% of the questions (i.e., 6 or more questions out of 21) with a missing score at a given visit, then the total score will be set to missing.

5.8 Acne, Hirsutism, Peripheral Edema, and Other Clinical Signs and Symptoms of Cushing's Syndrome – Calculation of Total Scores

Acne Global Score

A total of six locations (Forehead, Right Cheek, Left Cheek, Nose, Chin, and Chest and Upper Back) are evaluated with the following grading scale, depending on the severity of the acne: 0 - No Lesions, 1 – One or more comedones, 2 – One or more papules, 3 – One or more pustules, 4 – One or more nodules. The following Factor is assigned to the locations of the lesion(s) as follows: 2 – Forehead, 2- Right Cheek, 2- Left Cheek, 1 – Nose, 1 – Chin and 3 - Chest and Upper Back.

The score for each location (local score) is calculated using the formula:

Local score = Factor × Grade (0-4)

The global score is the sum of local scores as follows:

Global score = Sum (all local scores)

The global score can range from 0 to 44. If one location has a missing local score, then the missing local score will be imputed as the average of the non-missing local scores for that location. If more than 25% of locations (i.e., 2 or more locations out of 6) are missing a local score, then the global score will be set to missing.

Hirsutism Total Score (for females only)

Hirsutism will be assessed for females only. The total score is the sum of all the scores obtained in each of the 9 locations assessed (Upper Lip, Chin, Chest, Abdominal, Pubic, Arm, Thigh, Back, Buttocks). Each location is graded from 0 for no hirsutism to 4 for frank virilization. Total score can vary between 0 and 36. A high score means that the hirsutism is more visible. If one or two locations have a missing score, then the missing score will be imputed as the average of the non-missing scores for that location in the ITT population. If more than 25% of the locations (i.e., 3 or more locations out of 9) are missing a location score, then the total score will be set to missing.

Peripheral Edema Total Score

The total score is the sum of all the scores obtained in each of the 3 locations (Lower calf at 7 cm proximal to the midpoint of the medial malleolus; behind the medial malleolus; and dorsum of the foot). Each location is graded from 1 (barely detectable) to 4 (>30 seconds to rebound). Total score can range between 0 and 12. A high score means that the edema is more pronounced. If one or more locations has a missing score, then the total score will be set to missing.

Total Score for the Other Clinical Signs and Symptoms of Cushing's Syndrome

The other clinical signs and symptoms, defined in Appendix L of the protocol, are moon facies, facial plethora, striae, bruising, supraclavicular fat, irregular menstruation (females only), and dysmenorrhea (females only). Each sign/symptom, if present, is graded as Mild (=1), Moderate (=2), or Severe (=3). If not present, the sign/symptom is graded as None (=0). If the irregular menstruation or dysmenorrhea grade is missing for a female subject who is post-menopausal or surgically sterile, the missing grade will be set to 0.

Two total severity scores will be calculated as follows:

The Total Signs Score is the sum of the severities for the first 5 clinical signs assessed by the investigator (moon facies, facial plethora, striae, bruising, and supraclavicular fat). This total score can range from 0 (none) to 15 (worst). If 2 or more of the individual signs have missing scores at a given visit for a subject, then the Total Signs Score will be set to missing. If at least 4 of 5 individual signs are actually assessed, the Total Signs Score will be standardized by dividing it by the number of non-missing individual signs and then multiplying by 5.

The Menstrual Abnormalities Total Score is the sum of the severities for the last 2 subject-reported symptoms (for females only: irregular menstruation and dysmenorrhea). This total score can range from 0 (none) to 6 (worst). If either of the two individual symptoms has a missing score at a given visit for a subject, then the Menstrual Abnormalities Total Score will be set to missing.

5.9 Handling of Missing Data

Missing or Inadequate UFC/LNSC Collections

Refer to Section 5.4 and Section 5.5 for the handling of missing or inadequate UFC/LNSC collections.

Handling of Missing Data for the Analysis of Exploratory Efficacy Endpoints by Visit

For exploratory efficacy endpoints assessed at multiple visits, at-visit analyses will be performed using by-visit univariate methods. Imputation of a missing endpoint value for a subject at a visit may be applied as part of supportive or sensitivity analyses. Any imputation used for these purposes will be reported in the Clinical Study Report.

Partially Missing Data for Triplicate Measurements of Blood Pressure and Heart Rate

Refer to Section 5.6 for the handling of partially missing data for triplicate measurements of blood pressure and heart rate.

Partial and Missing Dates

Imputations of missing and partial dates are to be used only for the following: assessment of treatment emergence status of an AE and determination of study day of onset and duration of the AE (if applicable); for definitions of prior and concomitant medications; and for calculation of time since diagnosis of historical conditions of interest (e.g., CS).

Missing or Partial Adverse Event and Prior/Concomitant Medication Start Dates

- If the day is missing but both the month and year are non-missing, then the missing day will be imputed as 01. For an AE, however, if the month and year are the same as the month and year of the date of the first dose of levoketoconazole, then the missing day will be imputed to be the day part of the first dose date.
- If both the day and month are missing but the year is non-missing, then the missing day and month will be imputed as 01JAN. For an AE, however, if the year is the same as the year of the date of the first dose of levoketoconazole, then the missing day and month will be imputed to be the day and month parts of the first dose date.
- If the date is completely missing, then the start date will be imputed to be the earlier of the date of the first dose of levoketoconazole and the AE or medication end date. If the end date is partial, then impute the end date first before imputing the start date.

Missing or Partial Adverse Event and Prior/Concomitant Medication End Dates

If the AE or medication is reported as ongoing (or for an AE, not resolved/not recovered or recovering/resolving), then the end dates should be blank; otherwise, the following rules for imputation should be followed:

- If the day is missing but both the month and year are non-missing, then the missing day will be imputed as the last day of the month.
- If both the day and month are missing but the year is non-missing, then the missing day and month will be imputed as 31DEC. For an AE, however, if the year is the same as the year of the date of the last dose of levoketoconazole, then the missing day and month will be imputed to be the day and month parts of the last dose date.
- If the date is completely missing, then the end date will be imputed to be the date of the first scheduled visit that is after the AE or medication start date or the subject's last dose date, if there is no scheduled visit that is after the AE or medication start date. If the start date is partial, then impute the start date first before imputing the end date.

If the imputation rules above result in an end date being earlier than the start date, where one or both dates are imputed, the original dates and the imputed dates will be reviewed by the study statistician to adjust the imputed dates just enough to make the end date no earlier than the start date without changing the non-missing parts of a partial date.

Missing or Partial Diagnosis Dates of Historical Conditions of Interest

- If the day is missing but both the month and year are non-missing, then the missing day will be imputed as 01.
- If both the day and month are missing but the year is non-missing, then the missing day and month will be imputed as 01JAN.
- If the date is completely missing, then it will not be imputed.

6. Statistical Methods

6.1 General Principles

All data processing, summarization and analyses will be performed using SAS Version 9.4 or later of the SAS® statistical software package.

The following principles will be applied to all TFLs unless otherwise stated in later parts of this SAP.

Table 4 General Principles for the Presentation of Results in Tables, Figures, and Listings

	Principles or Values
Visit labels and order presented	Original Baseline, OLE Screening (in listings only), OLE Baseline, Month 3, Month 6, Month 9, … Month 36, End of Study, Worst (post-Baseline) Result (for shift or threshold analyses of safety endpoints and summaries of continuous endpoints, where applicable).
Tables and Figures	Data (except for AEs) in summary tables and figures will be presented by visit for all subjects. In addition, there will be summaries for the End of Study visit, where subjects will be summarized by dose level received at the last visit, for each of the subgroups below: - Subjects with total days on levoketoconazole >=80 days (all subjects) - Subjects with total days on levoketoconazole >=18 months - Subjects with total days on levoketoconazole >=30 months For AEs only: Data in summary tables will be presented by the levoketoconazole dose received at the day of onset of the AE.
Listings	All data collected, as well as derived data used in the analyses, will be presented in listings by site, subject, and visit (where applicable), unless otherwise specified.
Units for quantitative measures	All laboratory test results received from the local and central laboratories will be provided in both International System of Units (SI) and conventional units (if available). For the TFLs, the results will be summarized or presented in SI units (conversion will be made if results were only available in conventional units), with one exception. For HbA1c, the results will be summarized in tables and figures and presented in listings in conventional unit (i.e., in %). Laboratory test results received from local laboratories will be presented in listings only and not included in the tables

	Principles or Values
	and figures. Refer to Appendix 1 for the SI unit corresponding to each laboratory test.
Precision levels for laboratory values	Refer to Appendix 2 for the precision level in which each laboratory test is reported by the central laboratories.
Descriptive summary statistics for continuous variables	Number of subjects/observations (n), mean, standard deviation (SD), standard error (SE; where applicable), median, minimum, and maximum For a numeric result presented in the database with a "<", "≤", ">", or "≥" preceding the number, the value at (if "≤" or "≥") or just below (if "<') or just above (if ">") the numeric part will be used in the summary. For example, if the result is "<5", and the data for the variable are measured to one decimal place, then the result will be summarized as 4.9.
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)], where percentages will be presented to one decimal place All categories specified in the table and figure shells will be presented in the actual tables and figures, even if frequency is zero; in this case, no percentage will be presented. Note that the terms "proportion" and "percentage" of subjects are used interchangeably in this SAP. In the descriptive summaries, percentages (e.g., 85.1%) will be presented rather than proportions (e.g., 0.851).
Denominator for percentages	Number of subjects in the analysis population, unless stated otherwise in table shell(s)
Include "Missing" as category	Yes, when the number missing is greater than zero, unless otherwise specified.
Display for 0 percentages	Blank
Display to the same number of decimal places as the collected value	Minimum Maximum
Display to one more decimal place than collected value	Mean Median Confidence Interval (CI)
Display to two more decimal places than collected value	SD SE
Limit of precision for displays	3 decimal places, unless otherwise specified
Date Format	DDMMMYYYY
Significance tests and CIs	Two-sided and use a 5% significance level

	Principles or Values
	P-values will be presented to four decimal places, except values that are less than 0.0001 will be presented as "<0.0001" and values that are greater than 0.9999 will be presented as ">0.9999".
Source footnotes	Each table will have a footnote that lists the source data listing(s). Each figure will have a footnote that list the source table(s), if available, or the source data listing(s), otherwise.
Dictionary names and versions	The dictionary names and versions will be included in a footnote in all medical history, AE, and prior or concomitant medication TFLs that present coded terms from the dictionaries.

6.2 Subject Disposition

The disposition summary for all subjects will include:

- number of subjects in the ITT and PP populations
- number and percentage of subjects who were treated, completed, and discontinued the study with discontinuation reasons
- number and percentage of subjects who completed each scheduled visit

A subject is considered to have been treated during the study when the subject has received at least one dose of levoketoconazole. Subjects who meet the following sponsor-defined conditions are considered study completers for the purposes of analysis:

- Subjects with Month 36 visit before 01 March 2022: If they completed the next scheduled visit (Month 39).
- All other subjects: If they completed the Month 36 visit or completed a scheduled visit within 3 months prior to 31 December 2022.

Subjects who discontinued study participation without meeting one of the conditions above are considered as discontinuing from the study (non-completers).

Subjects' parent study information will be tabulated, including subject completion status in SONICS and/or LOGICS, whether subject is levoketoconazole-naïve when entering LOGICS, and last study visit / last dose level in SONICS and/or LOGICS.

In addition, a separate summary will also be provided for each of the following categories for all screened subjects:

- Subject disposition for the screening period
- Subject counts by site, country, and region (United States [US], non-US)

6.3 Protocol Deviations

A summary of major protocol deviations (a subset of protocol deviations that may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being) will be presented by deviation category, subcategory, and the specific deviation description. Both major and minor deviations will be provided in a listing.

Protocol deviations due to COVID-19 illness and/or COVID-19 public health control measures will be summarized and listed separately.

6.4 Demographics and Other Background Characteristics

6.4.1 Demographics and Baseline Characteristics

Demographics, baseline, and disease characteristics will be summarized for both ITT and PP populations.

Standard descriptive statistics will be presented for the continuous variables of:

- age (years)
- OLE baseline weight (kg)
- OLE baseline height (cm)
- OLE baseline body mass index (BMI) (kg/m^2)
- time since diagnosis of CS (months)
- time since last surgery for the management of CS

The total counts and percentages will be presented for the categorical variables of:

- sex
- childbearing potential (females only)
- ethnicity
- race
- classification of CS
- prior treatment for CS (yes or no)
- OLE baseline glycemia status (pre-diabetic, normal, diabetic, as defined in Section 6.6.7)

6.4.2 Medical History

Medical history conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1. Medical history conditions will be summarized by system organ class (SOC) and preferred term (PT).

6.4.3 Prior and Concomitant Medications

Incidence of prior and/or concomitant medications will be presented by drug class (i.e., Anatomical Therapeutic Chemical (ATC) Level 3 classification). Coding will be done using the World Health Organization (WHO) Drug September 2018 dictionary.

Separate summaries for prior and concomitant medications will be presented by the four medication categories prespecified in the CRF, namely, anti-diabetic, anti-hypertensive, cholesterol medication, and Cushing's medication.

A medication record will be classified as either prior or concomitant according to the criteria below:

- Prior medications are medications taken (either started or ongoing) before the study and ended prior to the OLE Baseline visit.
- Concomitant medications are medications taken during the study, including those started before but ongoing at first dose (OLE Baseline visit), up through end of study.

In addition, new concomitant medications, defined as medications started on or after first dose (OLE Baseline visit), will be summarized.

Non-drug therapies given or procedures performed during the study will be listed only (i.e., no table).

6.5 Levoketoconazole Exposure and Compliance

Exposure to Levoketoconazole

The total levoketoconazole (i.e., levoketoconazole) duration (days) during this OLE study will be summarized under each dose level received as well as across all dose levels for all subjects. Total days on levoketoconazole, the cumulative dose of levoketoconazole (mg), and the average daily dose of levoketoconazole (mg/day) during this OLE study will be presented for all subjects.

In addition, pooled results from all three studies for total days on levoketoconazole will also be presented for all subjects as follows:

- Total days on levoketoconazole prior to OPTICS (SONICS and or LOGICS, where applicable)
- Total days on levoketoconazole, all three studies combined

- Total days on levoketoconazole – all three studies combined by duration category (frequencies of subjects, >=1 year, >= 2 years, >=3 years, >=4 years of exposure)

Similar summaries of total days on levoketoconazole will also be presented for subjects with continuous levoketoconazole exposure (i.e., continuous study participation in SONICS and/or LOGICS plus OPTICS).

Total levoketoconazole duration (days) will be calculated for each subject as the last levoketoconazole stop date minus first levoketoconazole start date plus one day.

Total days on levoketoconazole will be calculated for each subject as the actual total number of days the subject received levoketoconazole (i.e., gaps in levoketoconazole intake are not included in the calculation). If only one out of two daily dosing (i.e., A.M. or P.M. but not both) of the levoketoconazole is taken, it counts as 0.5 day.

Actual cumulative dose (mg) of levoketoconazole will be calculated as the total number of tablets dispensed minus the total number of tablets returned, then multiplying the result by 150 mg.

Average daily dose of levoketoconazole (mg/day) will be calculated as the actual cumulative dose of levoketoconazole divided by total levoketoconazole duration.

The levoketoconazole dispensing, accountability, as well as occurrence, timing, and reasons for dose discontinuations and dose increases will be displayed in listings.

Compliance to Levoketoconazole

Overall levoketoconazole compliance during this study will be calculated by dividing the actual cumulative dose of levoketoconazole (as described above) by the expected cumulative dose of levoketoconazole and multiplying the result by 100. The expected cumulative dose is first calculated at each dose level received (dose level x duration at current dose level) and then summed up across all dose levels.

Persistence with therapy will be assessed by the number and proportion of subjects who complete 1, 2, and 3 years of treatment (based on total days on levoketoconazole) in this study, with at least 80% compliance with levoketoconazole.

6.6 Efficacy

Descriptive summaries of all efficacy endpoints will be presented by visit, according to visit windows (as defined in Section 5.3), for all subjects combined and, where appropriate, by dose level (as described in Section 6.1) for the ITT population. For continuous variables, summaries will be presented for the observed values and for the absolute and percent changes from each of the Original and OLE Baselines (as defined in Section 5.1, where applicable) to each visit window. The 95% confidence interval

for the mean change and corresponding p-value will be calculated using paired t-test. For categorical variables, the shifts from each of the Original and OLE Baselines will be presented, where specified, and the shifts will be evaluated for significance using McNemar's test or Bowker test of symmetry.

The p-values from these comparisons will be used for descriptive purposes only, i.e., no statistical inferences will be made.

6.6.1 UFC and LNSC Analyses

mUFC Categorization Based on ULN

At each visit, the number and proportion of subjects in the following categories will be summarized for mUFC:

- mUFC less than or equal to the ULN
- mUFC above the ULN to 1.5X the ULN
- mUFC above 1.5X the ULN

Shifts from each of the Original and OLE Baselines will be evaluated using Bowker test of symmetry.

A separate mUFC analysis will be performed by summarizing the number and proportion of subjects in the following categories:

- mUFC less than or equal to the ULN (complete response)
- mUFC above the ULN to 1.5X the ULN and at least a 50% decrease from the Original Baseline (partial response)
- mUFC above 1.5X the ULN, or mUFC above the ULN to 1.5X the ULN without at least a 50% decrease from the Original Baseline (no response)

Shifts from each of the Original and OLE Baselines will also be evaluated using Bowker test of symmetry. Baseline results will be categorized as follows:

- mUFC less than or equal to the ULN
- mUFC above the ULN to 1.5X the ULN
- mUFC above 1.5X the ULN

In addition, proportion of subjects with mUFC less than or equal to the ULN will be compared between subjects with continuous exposure (defined as subjects who had no gap in study participation in SONICS and/or LOGICS and OPTICS) versus those with gaps between studies using Fisher's exact test.

LNSC Categorization Based on ULN

At each visit, the number and proportion of subjects in the following categories will be summarized for LNSC:

- LNSC less than or equal to the ULN
- LNSC above the ULN

Shifts from each of the Original and OLE Baselines will also be evaluated using McNemar's test.

Changes in mUFC and LNSC from Baseline

mUFC and LNSC will be summarized by visit, using descriptive statistics. Mean changes from Original Baseline and OLE Baseline will be assessed for nominal significance using paired t-test. For LNSC only, an analysis of covariance (ANCOVA) model will also be fitted with the change from the relevant Baseline in mean LNSC results at a post-baseline visit as the dependent variable, the result at the relevant Baseline as the independent variable, and the average collection time to midnight (in minutes) as covariate to assess the effect of collection time on the change from Baseline. Mean changes from each of the Original and OLE Baselines to each visit in mUFC will be compared between subjects with continuous exposure versus those with gaps between studies using unpaired t-test.

Line plots of the mean +/- SE of actual and change from each of the Original and OLE Baselines by visit will be produced for mUFC and LNSC.

mUFC Analysis on PP Population

All the analyses of mUFC as described above will also be conducted on the PP population as supportive analyses if the PP population is < 90% of the ITT population.

6.6.2 Clinical Signs and Symptoms

Clinical Signs and Symptoms Excluding Acne, Hirsutism and Peripheral Edema

The Total Signs Score and the Menstrual Abnormalities Total Score (see Section 5.8 for calculation detail) and changes from each of the Original and OLE Baselines will be summarized at each visit. Mean changes in the two total scores from each of the Original and OLE Baselines will be assessed for nominal significance using paired t-test.

Acne, Hirsutism and Peripheral Edema

Acne, hirsutism (for females only) and peripheral edema total scores and changes from each of the Original and OLE Baselines will be summarized at each visit. Mean changes in total score from each of the Original and OLE Baselines will be assessed for nominal significance using paired t-test.

Shifts from each of the Original and OLE Baselines for acne, hirsutism and edema total scores will also be summarized using the following categories and will be analyzed using Bowker test of symmetry:

- Acne global score: 0, 1-18, 19-44 (Doshi 1997) = none, mild, moderate to severe
- Hirsutism total score: 0-7, 8-15, 16-36 (Hatch 1981) = none to mild, mild to moderate, moderate to severe
- Peripheral edema total score: 0-3, 4-6, 7-12 = none to mild, mild to moderate, moderate to severe

Line plots of the mean +/- SE of actual and change from OLE Baseline values by visit will be presented.

6.6.3 Cushing's Syndrome Quality of Life Questionnaire

Cushing QoL total score (see Section 5.7 for calculation detail), subscale scores and the changes from each of the Original and OLE Baselines will be summarized at each visit, using descriptive statistics. Mean changes in total score from each of the Original and OLE Baselines will be assessed for nominal significance using paired t-test.

6.6.4 BDI-II

BDI-II total score and the changes from each of the Original and OLE Baselines will be summarized at each visit, using descriptive statistics. Mean changes in total score from each of the Original and OLE Baselines will be assessed for nominal significance using paired t-test.

In addition, the number and percentage of subjects by category of severity (Minimal Depression: total score 0-13; Mild Depression: 14-19; Moderate Depression: 20-28; Severe Depression: 29-63) will be summarized by visit.

6.6.5 CS Comorbidity Biomarkers and HOMA-%B

The observed value and the changes/percent changes from each of the Original and OLE Baselines in individual biochemical markers of CS comorbidities (fasting glucose, fasting insulin, HOMA-IR, HbA1c, blood pressure, total cholesterol, HDL-C, LDL-C, and hsCRP) will be summarized at each visit using descriptive statistics. Mean changes from each of the Original and OLE Baselines will be assessed for nominal significance using paired t-test. Mean changes from Original Baseline to each visit will also be compared between subjects with continuous exposure versus those with gaps between studies using unpaired t-test.

HOMA-IR is calculated by multiplying fasting plasma insulin (FPI, in microU/L)) by fasting plasma glucose (FPG, in nmol/L), then dividing by the constant 22.5, i.e., HOMA-IR = (FPI×FPG)/22.5. Subjects who are using insulin as a concomitant medication during the study will be excluded from fasting insulin and HOMA-IR summaries.

Homeostatic Model Assessment-Beta Cell Function (HOMA-%B) is calculated as (20 x FPI)/(FPG - 3.5) and will also be summarized at each visit. HOMA-%B is only calculated whenever FPI and FPG are collected on the same day. FPI and FPG from different days cannot be combined to calculate HOMA-%B. Subjects who are using insulin during the study will be excluded from all HOMA-%B summaries.

In addition, shifts from each of the Original and OLE Baselines (with regards to the laboratory reference ranges) in individual biochemical markers of CS comorbidities will be summarized at each visit, and analyzed using Bowker test of symmetry. Line plots of the mean +/- SE of actual and change from OLE Baseline values by visit will be presented.

6.6.6 Medication Changes

The number and proportion of subjects with usage of each of the concomitant medication categories (anti-diabetic, anti-cholesterol, and anti-hypertensive) at OLE Baseline will be summarized.

In addition, the number and proportion of subjects with medication changes from the OLE Baseline will be presented. Subjects whose usage is ongoing or started at the OLE Baseline will be categorized as follows:

1) New and clinically significant medication – New medication is started during the study and its use was potentially clinically significant
2) Medication dose increased – Dose is increased compared to the OLE Baseline AND the increase is considered potentially clinically significant
3) Medication dose restarted after a gap – The medication is stopped after the OLE Baseline but is restarted during the study AND the restart is considered potentially clinically significant
4) Clinically insignificant change in medication – The change represents either the same dose in a different formulation or a pharmaceutically equivalent dose of a different drug (i.e., a substitution)
5) No medication changes from the OLE Baseline
6) Medication dose decreased – Dose is decreased compared to the OLE Baseline AND the decrease is considered potentially clinically significant, or the dose is stopped after the OLE Baseline

New and clinically significant medication changes, medication dose increased or restarted after a gap, clinically insignificant change in medication, and medication dose decreased (Items #1,2,3,4,6 above) will be evaluated prior to the database lock by a medical monitor.

Subjects with no usage ongoing or started at the OLE Baseline will be categorized as follows:

1) Medication added after OLE Baseline
2) No medication used.

If a subject has more than one medication in the same medication class that falls under different usage categories above, the subject will be counted under the "worst" of these categories, i.e., the first applicable category that is listed above.

6.6.7 Subgroup Analyses

Subgroup analyses for mUFC Categorization based on ULN, changes in mUFC from Baseline, and changes in CS comorbidities biomarkers from Baseline will be performed for the following subgroups of subjects (with a minimum subgroup size of at least 15 subjects):

Prior Therapy for Cushing's Syndrome

Subgroup displays will be generated for subjects who had prior surgery, radiotherapy, or medication therapy for the management of CS, versus those without.

Baseline Glycemia Status

Subgroup displays will be generated for subjects who enter the study as pre-diabetic (OLE Baseline fasting glucose greater or equal to 100 mg/dL [5.6 mmol/L] and less than 126 mg/dL [7.0 mmol/L] without concomitant use of anti-diabetic medication) versus those with normal fasting glucose versus those who were diabetic (OLE Baseline fasting glucose ≥ 126 mg/dL or receiving anti-diabetic medications at OLE baseline).

If there are less than 15 subjects in the pre-diabetic subgroup, the pre-diabetic subjects and subjects with normal fasting glucose will be combined into one subgroup (non-diabetic) versus those in the diabetic subgroup.

Age

Subgroup displays will be generated for subjects with age < the median age (of the ITT population) versus those with age ≥ the median age.

6.7 Safety

Descriptive summaries of all safety endpoints, excluding AEs, will be presented by visit window (as defined in Section 5.3) for all subjects combined and where applicable, by dose level (as described in Section 6.1). For continuous variables, summaries will be presented for the observed values and for the absolute and percent changes from each of the Original and OLE Baselines.

The ITT population will be used for all safety analyses.

6.7.1 Adverse Events

All AEs will be collected from the date that informed consent was signed. Verbatim terms for each AE will be coded using MedDRA version 21.1 and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 [NCI CTCAE, 2010].

Table 5 The Severity of AEs and SAEs per NCI CTCAE, Version 4.03

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

An AE of scientific and medical concern specific to the study treatment will be identified as an AESI. AESIs will be reported regardless of seriousness or causality. There are 3 types of AESIs: Persistent QTc prolongation, Potential hepatic events, and Adrenal insufficiency.

All AE summaries will be restricted to Treatment-Emergent AEs (TEAEs), which are defined as those AEs with an onset on or after the date of the first levoketoconazole dose in this study and up to 30 days after the last dose of levoketoconazole.

TEAEs will be summarized by dose level (i.e., the last dose level on or before the AE onset date) and overall.

The number and percentage of subjects will be summarized by SOC and PT and will be ordered by descending order of incidence of SOC and PT within each SOC. A subject with more than one occurrence of the same TEAE in a particular SOC or PT will be counted only once in in that particular SOC or PT. If a subject experiences the same TEAE at more than one level of severity, or with more than one level of relationship

to levoketoconazole, the most severe rating or the stronger causal relationship to levoketoconazole will be used.

The following TEAE summaries will be produced:

- For the overview summary of all TEAEs - Total number of TEAEs, number of subjects with at least one TEAE, number of subjects with at least one treatment-emergent SAE, number of subjects with at least one TEAE with special interest, number of subjects with at least one serious TEAE of special interest, number of subjects with at least one severe TEAE (CTCAE grade =3), number of subjects with at least one life-threatening TEAE (CTCAE grade =4), number of subjects with at least one TEAE leading to discontinuation of levoketoconazole, and number of subjects with at least one TEAE leading to death. For the number of TEAEs, a unique event for a subject is defined as a unique combination of SOC, PT, onset date, CTCAE grade, and relationship to levoketoconazole.
- For the overview summary of all levoketoconazole-related TEAEs – Same as in the previous bullet point.
- For the overview summary of all TEAEs, by time of first onset category (in 6-month intervals, i.e., 0 – 6 months; > 6 months – 12 months; > 12 months – 18 months; etc. Categories may be combined at the discretion of the sponsor depending on actual subject counts.)
- Number of subjects with TEAEs by MedDRA SOC and PT.
- Number of subjects with TEAEs by MedDRA SOC, PT, and closest relationship to levoketoconazole (Related/Not Related). Related events are defined as events that are definitely or probably related to levoketoconazole. AEs with a missing relationship are considered definitely related. At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported one or more events.
- Number of subjects with TEAEs by MedDRA SOC, PT, and worst reported severity. Worst severity is defined as first Death, then life-threatening followed by Severe, Moderate, and Mild in that order. AEs with missing severity are categorized as severe in the TEAE summary tables. At each level of subject summarization, a subject is classified according to the worst severity if the subject reported one or more events.
- Number of subjects with treatment-emergent SAEs by MedDRA SOC and PT.
- Number of most common TEAEs, i.e., unique events or episodes (frequency above 5% of all subjects) and incidence rate per subject-month (defined as the number of TEAEs divided by the total subject-months on levoketoconazole) by MedDRA SOC and PT.

- Number of subjects with TEAEs, by time of first onset category (in 6-month intervals, i.e., 0 – 6 months; > 6 months – 12 months; > 12 months – 18 months; etc. Categories may be combined at the discretion of the sponsor depending on actual subject counts.), MedDRA SOC and PT.
- Number of subjects with TEAEs of special interest (AESI) by category, MedDRA SOC and PT. The AESI categories are QTc prolongation, potential hepatic events, and adrenal insufficiency.
- Number of subjects with serious TEAEs of special interest by AESI category, MedDRA SOC and PT.
- Number of subjects with TEAEs leading to levoketoconazole discontinuation by MedDRA SOC and PT.

Listings of all AEs, SAEs, AESIs, AEs leading to discontinuation of levoketoconazole, AEs leading to withdrawal from the study, and AEs leading to death will be presented by subject, detailing verbatim term given by the Investigator or designee, SOC, PT, onset date, resolution date, severity, seriousness, AESI category, action taken, outcome, and levoketoconazole relatedness. The event onset will also be shown relative (in number of days) to date of first dose.

TEAE summaries by subgroups of interest will be performed as described in Section 6.7.7.

6.7.2 Laboratory Evaluations

The following safety laboratory analytes will be analyzed:

Liver Function Tests: Aspartate Aminotransferase (AST) (SGOT), Alanine Aminotransferase (ALT) (SGPT), Gamma-glutamyl transferase (GGT), Alkaline phosphatase (ALP), Lactate dehydrogenase (LDH), Direct and Total bilirubin.

Hematology: Platelet Count, Red Blood Cell (RBC) Count, White Blood Cell (WBC) Count (absolute), Hemoglobin, Hematocrit, RBC indices (Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC)), WBC Differentials (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils).

Clinical Chemistry, excluding Liver Function Tests: Blood Urea Nitrogen, Creatinine, Sodium, Potassium, Chloride, Total Carbon Dioxide (CO_2), Calcium, Magnesium, Phosphate, Uric Acid, Albumin, and Total Protein.

Urinalysis: Specific gravity, pH, glucose, protein, blood, and ketones. In addition, microscopic examination if blood or protein is > trace positive by dipstick.

Safety Hormones and Biomarkers: Thyroid-Stimulating Hormone (TSH)/Free T4, LDL-C:HDL-C ratio, Triglycerides

Other Laboratory Tests: Serum cortisol, ACTH

Laboratory results will be summarized by SI units (see Section 6.1). Results will be summarized as received from the central laboratory. In the case that the results in SI units were not provided, data conversions will be performed. For serum cortisol only, an ANCOVA model will also be fitted with the change from the relevant Baseline in serum cortisol results at a post-baseline visit as the dependent variable, the result at the relevant Baseline as the independent variable, and the collection time since 8:00 (in minutes) as covariate to assess the effect of collection time on the change from Baseline.

Descriptive summaries by visit, including observed values and change from Original Baseline and OLE Baseline values, will be produced for each laboratory test.

Shifts (low/normal/high) from baseline tables based on the reference ranges will be constructed. The shifts will be from each of the Original and OLE Baselines to each post-Baseline visit, and to the worst post-Baseline results during the study.

For LFTs, tables will also be created to summarize the incidence at each visit and the shifts from Original Baseline and OLE Baseline for ALT, AST, and total bilirubin (similar to the shifts described above) using the following categories:

ALT and AST: <LLN, within the normal range, > ULN and ≤ 3X ULN, > 3X ULN to ≤ 5X ULN, > 5X ULN to ≤ 10X ULN and > 10X ULN.

Total bilirubin: <LLN, within the normal range, > ULN and ≤ 1.5X ULN, >1.5X ULN and ≤2X ULN, and >2X ULN.

An evaluation of drug-induced serious hepatotoxicity (eDISH) plot will be produced to assess the liver enzyme abnormalities that occur. ALT, AST, and Total bilirubin will be plotted as multiples of the ULN, on a logarithmic scale. Those results that are greater than 2x ULN for Total bilirubin and greater than 3x ULN for ALT (or AST) will be easily identified through the use of reference lines. The following 6 eDISH plots will be produced with the first variable on the x-axis and the second variable on the y-axis, and where the Baseline is the relevant Baseline being plotted:

- Baseline ALT (expressed as x ULN) x Maximum Post-baseline ALT (expressed as x ULN)
- Maximum Post-baseline ALT (expressed as x ULN) x Maximum Post-baseline AST (expressed as x ULN)
- Maximum Post-baseline ALT (expressed as x ULN) x Maximum Post-baseline Total Bilirubin (expressed as x ULN)

- Baseline AST (expressed as x ULN) x Maximum Post-baseline AST (expressed as x ULN)
- Maximum Post-baseline AST (expressed as x ULN) x Maximum Post-baseline Total Bilirubin (expressed as x ULN)
- Baseline Total Bilirubin (expressed as x ULN) x Maximum Post-baseline Total Bilirubin (expressed as x ULN)

Box and whisker plots presenting actual and change from Baseline values in the three LFTs for each visit will be produced.

Potential clinically significant (PCS) results for selected laboratory tests will be listed, according to the criteria listed in Table 6 below:

Table 6 Laboratory Test PCS Criteria

Category	Analyte	PCS Criteria – Conventional Units	PCS Criteria – SI Units
Hematology	Eosinophils	≥ 700/µL	≥ 0.7×10^9/L
	Hematocrit (Hct)	Female: ≤ 32%; Male: ≤ 37%	Female: ≤ 0.32; Male: ≤ 0.37
	Hemoglobin (Hgb)	Female: ≤ 9.5 g/dL; Male: ≤ 11.5 g/dL or decrease of ≥ 20%	Female: ≤ 95 g/L; Male: ≤ 115 g/L or Decrease of ≥ 20%
	Leukocytes	Low: ≤ 2800/ µL High: ≥ 16000/µL	Low: ≤ 2.8×10^9/L High: ≥ 16×10^9/L
	Neutrophils	≤ 1000/µL	≤ 10^9/L
	Platelets	Low: ≤ 75×10^3/µL High: ≥ 700×10^3/µL	Low: ≤ 75×10^9/L or High: ≥ 700×10^9/L
Blood Chemistry	Albumin	< 2.5 g/dL	< 25 g/L
	Blood Urea Nitrogen (BUN)	> 30 mg/dL	> 10.71 mmol/L
	Calcium	Low: < 7 mg/dL; High: > 12 mg/dL	Low: < 1.75 mmol/L; High: > 3 mmol/L
	Cholesterol	> 300 mg/dL	> 7.76 mmol/L
	Creatinine	> 2 mg/dL	> 176.8 µmol/L
	Glucose	Low: < 50 mg/dL;	Low: < 2.8 mmol/L;

Category	Analyte	PCS Criteria – Conventional Units	PCS Criteria – SI Units
		High: >250 mg/dL	High: >13.9 mmol/L
	LDH	> 3x ULN	> 3x ULN
	Phosphate	Low: < 2.0 mg/dL; High: > 5.0 mg/dL	Low: < 0.65 mmol/L; High: > 1.62 mmol/L
	Potassium	Low: < 3.0 mEq/L; High: > 5.5 mEq/L	Low: < 3.0 mmol/L; High: > 5.5 mmol/L
	Sodium	Low: < 130 mEq/L; High: > 150 mEq/L	Low: < 130 mmol/L; High: > 150 mmol/L
	Triglycerides	High: > 500 mg/dL	> 5.65 mmol/L
	Uric Acid	Female: > 8.0 mg/dL; Male: > 10.0 mg/dL	Female: > 475.8 µmol/L; Male: > 594.8 µmol/L
Liver Safety	ALT	High: > 3x ULN	High: > 3x ULN
	ALP	High: > 3x ULN	High: > 3x ULN
	AST	High: > 3x ULN	High: > 3x ULN
	Total Bilirubin	High: > 2x ULN	High: > 2x ULN
	GGT	High: > 3x ULN	High: > 3x ULN
Urinalysis	Blood	Increase of ≥ 2 units	
	Glucose	Increase of ≥ 2 units	
	Protein	Increase of ≥ 2 units	

ACTH

All summaries for ACTH will be presented for subjects with CD only. In addition to the summaries described above for laboratory tests in general, the following will be done for ACTH:

- ACTH will be transformed to fold-ULN (i.e., multiples of the ULN) and summaries of ACTH as fold-ULN will be produced.
- The mean changes from Original Baseline and OLE Baseline to each visit will be assessed for nominal significance using paired t-test.
- Subgroup summary: ACTH summary of actual value and change from Original Baseline and OLE Baseline will be presented by sex (also stated in Section 6.7.7).

- Needle plots of individual subject ACTH values plotted as fold-ULN from OLE Baseline to the end of study will also be produced.

6.7.3 Vital Signs

Descriptive summaries by visit, including observed values and change from Original Baseline and OLE Baseline values, will be produced for vital signs (heart rate, weight, BMI, and temperature).

Shifts from baseline tables based on the categories of vital sign clinical importance criteria (as presented in Table 7 below) will be constructed. The shifts will be from Original Baseline and OLE Baseline to each post-Baseline visit, and to the worst post-Baseline results during the study.

Table 7 Vital Sign Clinical Importance Criteria

Vital Sign	Criteria	Flag
Heart Rate (HR)	below 44 bpm	Low (L)
	44-100 bpm	Normal
	101-120 bpm	High (H)
	above 120 bpm	Very High (VH)
Systolic Blood Pressure (SBP)	below 90 mm Hg	Low (L)
	90-139 mm Hg	Normal
	140-169 mm Hg	High (H)
	170 mm Hg and above	Very High (VH)
Diastolic Blood Pressure (DBP)	below 50 mm Hg	Low (L)
	50-89 mm Hg	Normal
	90-109 mm Hg	High (H)
	110 mm Hg and above	Very High (VH)

Shifts from Original Baseline and OLE Baseline in blood pressure classification as defined in Table 8 below, will be summarized in the same manner as described above for the shifts based on vital sign values of clinical importance.

Table 8 Blood Pressure Classification (Adults Over 18 Years of Age)

Blood Pressure Classification	
SBP (mmHg)	**DBP (mmHg)**
< 120	and < 80
120-139	or 80-89
140-159	or 90-99
≥ 160	or ≥ 100

Subjects with PCS results in vital signs will be listed, according to the criteria listed in Table 9 below:

Table 9 Vital Sign PCS Criteria

Vital Sign Parameters	PCS Criteria
Pulse	Increase of ≥ 15 bpm from baseline and ≥ 120 bpm
	Decrease of ≥ 15 bpm from baseline and ≤ 50 bpm
Systolic Blood Pressure	Increase of ≥ 20 mmHg from baseline and ≥ 180 mmHg
	Decrease of ≥ 20 mmHg from baseline and ≤ 90 mmHg
Diastolic Blood Pressure	Increase of ≥ 15 mmHg from baseline and ≥ 105 mmHg
	≤ 50 mmHg
Temperature	Increase of ≥ 2.0 °C from baseline and ≥ 38.0 °C
Weight	Decrease of ≥ 10% from baseline
	Increase of ≥ 10% from baseline

6.7.4 Electrocardiograms

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

- heart rate (bpm);
- PR interval (msec);
- QRS interval (msec);
- Bazett corrected QT (QTcB) interval (msec)
- Fridericia corrected QT (QTcF) interval (msec)
- RR interval (msec);

Descriptive summaries by visit, including observed values and change from Original Baseline and OLE Baseline values, will be produced for the quantitative ECG measurements listed above and the qualitative overall ECG interpretation (normal versus abnormal).

The number and percentage of subjects by category of QTc interval of potential clinical importance, presented in Table 10, will be summarized by visit. The worst categorical actual post-Baseline and worst categorical change from Original Baseline and OLE Baseline in post-Baseline values will be summarized. Using the categories for actual values, shift from baseline tables will be constructed. The shifts will be from Original Baseline and OLE Baseline to each post-Baseline visit and to the worst post-Baseline results during the study.

ECG readings that have been rejected after Spaulding central reader review will not be included in any analysis tables.

Table 10 QTcF Interval of Potential Clinical Importance Criteria

QTcF Interval	Criteria (msec)
Increase from Baseline	below 30
	30-60
	above 60
Actual Value	<=450
	451-480
	481-500
	above 500
Actual Value by Sex	>450 for Males >470 for Females

Subjects with PCS results in ECGs will be listed, according to the criteria listed in Table 11 below:

Table 11 ECG PCS Criteria

Parameter	Criteria
QTcF	Female: > 470 msec
	Male: > 450 msec
PR Interval	> 200 msec
Heart Rate	< 48 bpm
	> 96 bpm

6.7.5 Pituitary Magnetic Resonance Imaging

The results from the pituitary magnetic resonance imaging (MRI) will be summarized for subjects with a history of a pituitary tumor. The number and percentage of subjects with macroadenoma and those with microadenoma will be summarized at OLE Baseline and each post-baseline visit. The observed values in pituitary tumor size (in millimeters of maximum diameter), tumor height (sagittal and coronal views), tumor length (sagittal view), and tumor width (coronal view) and the changes in these values from Original Baseline and OLE Baseline to each post-baseline visit will be summarized.

The status of overall pituitary size and the status of pituitary tumor size/activity from OLE Baseline to each post-baseline visit will be summarized separately by radiologist assessment and by imputed categories as follows:

Radiologist assessment: Increase, Stable, Decrease, Unknown or Not Measurable, and Not Applicable (as collected on the CRF)

Imputed categories based on maximum tumor diameter: Increase (increase of +2mm or more from OLE Baseline result); Decrease (decrease of -2mm or more from OLE Baseline result); Stable (less than 2mm change in either direction); Unknown or Not Measurable (results unknown, or the tumor is not measurable).

The basis of tumor status assessment will also be summarized with the categories as follows: a) Overall tumor appearance change; b) Maximum tumor diameter change; c) Inference from pituitary gland change; Both a) and c); Both b) and c); Each of a), b), and c); No change; and Not applicable.

6.7.6 Physical Examinations

Physical examination results will be presented in a listing only (i.e., no table).

6.7.7 Subgroup Analyses for Safety

The following safety summaries will be produced for side-by-side comparison of subjects with continuous exposure versus those with gaps between studies:

- Overview summary of all TEAEs and summary of TEAEs by MedDRA SOC and PT (see Section 6.7.1)
- Mean changes from Original Baseline and OLE Baseline to each visit in LFTs, with between-group comparison using unpaired t-test
- Shift from the original Baseline and OLE Baseline in ALT, AST, and Total bilirubin using the categories defined in Section 6.7.2
- Mean changes from Original Baseline and OLE Baseline to each visit in ACTH, with between-group comparison using unpaired t-test
- Mean changes from Original Baseline and OLE Baseline to each visit in BMI and weight, with between-group comparison using unpaired t-test.
- Mean changes from Original Baseline and OLE Baseline in pituitary tumor size (in millimeters of maximum diameter) to each visit, with between-group comparison using unpaired t-test.

The same set of summaries for TEAEs overview, TEAEs by SOC and PT, and QTc intervals will be produced for subgroups of subjects (with a minimum subgroup size of at least 15 subjects) based on the following:

- Baseline glycemia status (pre-diabetic, diabetic, normal, as defined in Section 6.6.7)

- Age (<median age of the ITT population versus ≥ median age)

Descriptive summaries by subgroup of interest will be produced for the following laboratory tests: ACTH by sex (for the subset of subjects with CD only).

6.8 Interim Analysis

No interim analysis is planned for this study.

7. Changes from Planned Analyses in the Protocol

7.1 Imputation

Protocol Section 12.4.1 stated that "*Imputation may be performed for some endpoints as part of supportive or sensitivity analyses. Details of such imputations will be described in the SAP.*" However, in this SAP we did not predefine these imputations. Instead, it is stated in Section 5.9 that "Imputation of a missing endpoint value for a subject at a visit may be applied as part of supportive or sensitivity analyses. Any imputation used for these purposes will be reported in the Clinical Study Report."

7.2 UFC Adequacy

Protocol Section 12.6.1 stated that "*The mUFC will be calculated only if there are at least two adequate samples. The mUFC from the collections at each visit will be used in the analysis of UFC unless only one adequate sample is available, in which case the single sample will substitute for the mUFC.*" However, in this SAP, we require at least two adequate samples in order for mUFC to be calculated, which is consistent with the analysis method in LOGICS. If there is only one adequate sample, the mUFC will be missing.

7.3 Efficacy Analysis

Protocol Section 12.6 stated that "The 95% confidence interval for the difference in the paired proportions will be calculated using the adjusted Wald method, …". However, in this SAP we did not plan to calculate the 95% confidence interval for the difference in the paired proportions.

7.4 Subgroup Analyses

Protocol Section 12.7 stated that "*Subgroup analyses for selected exploratory efficacy endpoints and safety endpoints will be performed for a minimum subgroup size of at least 15 subjects. The subgroups of interest will include, but not be limited to, subgroups based on diagnosis of CD, prior therapy for CS, hypertension at Baseline, and prediabetes or diabetes at Baseline."* However, for "*diagnosis of CD*" and "*hypertension at Baseline"*, at least one of the subgroups' sizes is less than 15, thus the corresponding subgroup analyses are not planned to be performed.

7.5 Clinical Signs and Symptoms

Protocol Section 12.6.2 stated that "*Individual clinical signs and symptoms, ... will be summarized at each time point for assessment by number and percent of subjects.*" It is also stated that for signs and symptoms other than acne, hirsutism, and edema, "*Total severity score and changes from Baseline of the severity total score will be presented by visit."* However, in Section 5.8 of this SAP, it is clarified that only acne, hirsutism, and edema will be summarized by each of their total scores. For other signs and symptoms, instead of being summarized by one total severity score, two total scores (The Total Signs Score and the Menstrual Abnormalities Total Score) are defined to distinguish signs that are common to both males and females from those that apply to females only (menstrual abnormalities).

In the same section of the protocol, it is also stated that "*..shift tables in individual clinical signs and symptoms from each Baseline will be created to demonstrate any changes during the course of treatment…*"**.** However, based on the results from LOGICS, the sponsor found that the shift from Baseline analyses was not informative and will not be performed in this study.

7.6 Medication Changes

Protocol Section 12.6.6 stated that " *The number and proportion of usage of each medication class of interest at Baseline and at all post-Baseline visits by treatment will be displayed."* Since this is a single-arm study, the "by treatment" statement is an error in the protocol and should be ignored. In addition, the number and proportion of usage will be displayed for the OLE Baseline only.

In the same section, it is also stated that "*In addition, the number and proportion of subjects with medication changes during the study will be summarized by time point…*" However, only medication change assessments from OLE Baseline to the worst change post-OLE Baseline were defined and planned in this SAP.

7.7 Electrocardiograms

Protocol Section 12.5.5 stated that "*Summary ECGs,… will be summarized descriptively by dose and time point.*" However, ECG results by dose level will be presented at the End of Study time point only, as stated in Section 6.1.

This SAP also includes a PCS criterion for QTcF interval that is by sex: >450 msec for males; >470 msec for females, which is not mentioned in the protocol.

7.8 Interim Analysis

Protocol Section 12.5 stated that *" Interim analyses of safety will be performed and reported on a limited basis to satisfy requirements of study oversight, for example to IRB/IEC and Competent Authorities. These analyses may include the worsening of any TEAEs relative to the original parent study and relative to the OLE Baseline. The effect of cumulative dose and levoketoconazole treatment exposure may be evaluated as risk factors for increased AE incidence and severity. These limited analyses (e.g., common adverse reactions summary) will not be accompanied by assessments of potential benefits. Any unplanned interim efficacy analyses will be accompanied by unplanned interim safety analyses."* However, other than the periodic safety updates required by Competent Authorities and annual updates to the Investigator Brochure, no interim analysis of the data from this study will be performed.

8. References

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4 ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

9. APPENDIX 1 Safety Laboratory and Vital Signs Tests – Identifying Worst Values

The table below presents the direction of interest in determining the worst values for safety laboratory tests.

Laboratory Test	Direction of interest for worst case values	Direction to choose in case of both Low and High Values
HEMATOLOGY		
Hemoglobin	Low and High	Low
Hematocrit	Low and High	Low
RBC Count	Low and High	Low
MCV	Low and High	Low
MCH	Low	
MCHC	Low and High	Low
WBC Count	Low and High	Low
Basophils	High	
Eosinophils	High	
Neutrophils	Low and High	Low
Monocytes	High	
Lymphocytes	Low and High	High
Platelet Count	Low and High	Low
CHEMISTRY		
Calcium	Low and High	High
Magnesium	Low	
Phosphate	Low	
Sodium	Low and High	High
Potassium	Low and High	Low
BUN (Blood Urea Nitrogen)	Low and High	High
Creatinine	High	
Albumin	Low	
Chloride	Low	
Total CO2	High	
Uric Acid	High	
Total Protein	Low and High	Low
LIVER SAFETY TESTS		
AST (SGOT)	High	
ALT (SGPT)	High	
GGT	High	
AP	High	
Direct Bilirubin	High	
Total Bilirubin	High	
LDH	High	
SAFETY HORMONES AND BIOMARKERS		
TSH	Low and High	Low

Laboratory Test	Direction of interest for worst case values	Direction to choose in case of both Low and High Values
Free T4	High	
HDL-C	Low	
LDL	High	
LDL-C:HDL-C (ratio)	High	
Total Cholesterol	High	
Triglycerides	High	
hsCRP	High	
URINALYSIS		
Specific Gravity	Low and High	Low
pH	Low and High	Low
OTHER MEASURES		
Serum Cortisol	High	
ACTH	High	

The table above will be used in determining the worst values for safety laboratory tests within a visit window for a subject (see Section 5.3). If there are multiple such values for a laboratory test, then the worst value will be identified as follows:

- If all values are within the normal range (NR), then the lowest one will be used if 2nd column = Low. The highest one will be used if 2nd column = High. The one farthest from the midpoint of the NR will be used if 2nd column = Low and High. If two such values are equidistant from the midpoint, the lower one will be used if 3rd column = Low, and the higher one if 3rd column = High.
- If one or more values are within the NR and one value is outside the NR, then the value outside the NR will be used.
- If two or more values are outside the NR, then the lowest one among these will be used if 2nd column = Low. The highest one will be used if 2nd column = High. If the 2nd column = Low and High, then the lowest one will be used if 3rd column = Low, and the highest one if 3rd column = High.

The table below presents the direction of interest in determining the worst values for Vital Signs assessments tests.

Vital Signs Test	Direction of interest for worst case values	Direction to choose in case of both Low and High Values
HR	Low and High	Low
SBP	Low, High, and Very High	High
DBP	Low, High, and Very High	High
Temperature	High	

10. APPENDIX 2 Laboratory Tests – Precision Levels

Category	Analyte	SI Unit	Precision (Decimal Point)
Hematology	Hemoglobin	g/L	0
Hematology	Hematocrit	1	3
Hematology	RBC Count	10^{12}/L	1
Hematology	MCV	fL	1
Hematology	MCH	Pg	1
Hematology	MCHC	g/L	0
Hematology	WBC Count	10^9/L	1
Hematology	Basophils	%	1
Hematology	Abs. Basophils	10^9/L	2
Hematology	Eosinophils	%	1
Hematology	Abs.Eosinophils	10^9/L	2
Hematology	Neutrophils	%	1
Hematology	Abs.Neutrophils	10^9/L	2
Hematology	Monocytes	%	1
Hematology	Abs.Monocytes	10^9/L	2
Hematology	Lymphocytes	%	1
Hematology	Abs.Lymphocytes	10^9/L	2
Hematology	Platelet count	10^9/L	0
Chemistry	Calcium	mmol/L	2
Chemistry	Magnesium	mmol/L	2
Chemistry	Phosphate	mmol/L	2
Chemistry	Sodium	mmol/L	0
Chemistry	Potassium	mmol/L	1
Chemistry	Blood Urea Nitrogen (BUN)	mmol/L	1
Chemistry	Creatinine	µmol/L	1
Chemistry	Albumin	g/L	0
Chemistry	Chloride	mmol/L	0
Chemistry	Total CO2	mmol/L	0
Chemistry	Uric Acid	µmol/L	1
Chemistry	Total Protein	g/L	0
Liver Safety	LDH	U/L	0
Liver Safety	Total Bilirubin	µmol/L	1
Liver Safety	Direct Bilirubin	µmol/L	1
Liver Safety	AST(SGOT)	U/L	0
Liver Safety	ALT(SGPT)	U/L	0
Liver Safety	GGT	U/L	0
Liver Safety	AP	U/L	0
Liver Safety	LDH	U/L	0
Safety Hormones and Biomarkers	TSH	mU/L	2
Safety Hormones and Biomarkers	T-4 (Thyroxine) Free	pmol/L	1
Safety Hormones and Biomarkers	LDL-C:HDL-C (ratio)	Ratio	2
Safety Hormones and Biomarkers	Triglycerides	mmol/L	2

Category	Analyte	SI Unit	Precision (Decimal Point)
Safety Hormones and Biomarkers (CS Comorbidity)	Glucose, Plasma (Fasting)	mmol/L	1
Safety Hormones and Biomarkers (CS Comorbidity)	Insulin, Plasma (Fasting)	pmol/L	2
Safety Hormones and Biomarkers (CS Comorbidity)	HOMA-IR		1
Safety Hormones and Biomarkers (CS Comorbidity)	Hemoglobin A1C	%	1
Safety Hormones and Biomarkers	Total Cholesterol	mmol/L	2
Safety Hormones and Biomarkers (CS Comorbidity)	HDL-C	mmol/L	2
Safety Hormones and Biomarkers (CS Comorbidity)	LDL-C	mmol/L	2
Safety Hormones and Biomarkers (CS Comorbidity)	hsCRP	mg/L	1
Urinalysis	Specific Gravity		3
Urinalysis	pH		1
Other-Biochemical Marker	Serum Cortisol	nmol/L	1
Other-Biochemical Marker	ACTH	pmol/L	1
Disease Related (efficacy)	Cortisol, 24-hour	nmol/D	1
Disease Related (efficacy)	Mean Cortisol, 24-hour	nmol/D	1
Disease Related (efficacy)	Creatinine Excretion (Urine Creatinine)	nmol/D	1
Disease Related (efficacy)	LNSC	nmol/L	1