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GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CGI-S	Clinical Global Impression of Severity
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDS	Excessive Daytime Sleepiness
EOS	End-of-Study
EOT	End-of-Treatment
ESS	Epworth Sleepiness Scale
FCBP	Female of Childbearing Potential
FOSQ-10	Functional Outcomes of Sleep Questionnaire 10 Item Version
HbA1C	Hemoglobin A1C
ICH E3	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IH	Idiopathic Hypersomnia
IHSS	Idiopathic Hypersomnia Severity Scale
MedDRA	Medical Dictionary for Regulatory Activities
PGI-S	Patient Global Impression of Severity
PROMIS-SRI	Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment
PT	Preferred Term
SAP	Statistical Analysis Plan
SD	Standard Deviation
SIQ	Sleep Inertia Questionnaire
SOC	System Organ Class

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Abbreviation	Description
SOP	Standard Operating Procedure
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures, and Listings
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHODD	World Health Organization Drug Dictionary

1 PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures that will be produced, and the statistical methodologies that will be used are complete and appropriate to allow valid conclusions regarding the study objectives.

1.1 Responsibilities

Syneos Health will perform the statistical analyses of the safety and effectiveness data and is responsible for the production and quality control of all associated tables, figures, and listings (TFLs).

1.2 Timings of Analyses

Analyses will be conducted to support reporting requirements and other Sponsor requests. Final analyses will be conducted at the end of the study.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the long-term safety and effectiveness of pitolisant in patients with idiopathic hypersomnia (IH) who complete the Double-Blind Randomized Withdrawal Phase of Phase 3 study HBS-101-CL-010.

3 STUDY DETAILS/DESIGN

3.1 Brief Description

This is a Phase 3 open-label, long-term study to evaluate the long-term safety and effectiveness of pitolisant in adult patients with IH. Patients who complete the Double-Blind Randomized Withdrawal Phase of study HBS-101-CL-010 (i.e., completed the End-of-Treatment [EOT] Visit/Visit 5 in study

HBS-101-CL-010) and who meet the inclusion/exclusion criteria for study HBS-101-CL-011 are eligible for enrollment. Failure to comply with the Double-Blind Randomized Withdrawal Phase of study HBS-101-CL-010, as determined by the Medical Monitor, will preclude patients from participating in the open-label, long-term study.

The Screening Visit (Day -1) for this open-label, long-term study is the EOT Visit/Visit 5 from study HBS-101-CL-010; the results of assessments performed at this visit will be used to confirm patient eligibility. Patients will have up to 7 days from the EOT Visit/Visit 5 to enroll in study HBS-101-CL-011 and begin open-label pitolisant.

Enrolled patients may be titrated up to a maximum dose of 35.6 mg during a 3-week Titration Period (Day 1 to Day 21).

The results of assessments performed at the EOT Visit/Visit 5 (Day 84) of study HBS-101-CL-010 will be used as the Baseline values for this study.

Study HBS-101-CL-011 Protocol Section 2 provides a description of the study.

3.2 Patient Selection

3.2.1 Inclusion Criteria

Study HBS-101-CL-011 Protocol Section 4.1.1 specifies the inclusion criteria for the study.

3.2.2 Exclusion Criteria

Study HBS-101-CL-011 Protocol Section 4.1.2 specifies the exclusion criteria for the study.

3.3 Determination of Sample Size

[redacted]

3.4 Treatment Assignment and Blinding

All patients will take pitolisant. Blinding is not applicable in this open-label study.

3.5 Administration of Study Drug

Patients will take open-label pitolisant once daily in the morning upon wakening as detailed in Table 1.

Table 1: Pitolisant Dosing

3-Week Titration Period[a]			Long-Term Dosing Period[b]
Week 1 **(Days 1-7)**	**Week 2** **(Days 8-14)**	**Week 3** **(Days 15-21)**	**Week 4** **(Day 22 to End-of-Study [EOS])**
8.9 mg	17.8 mg	35.6 mg	8.9 mg to 35.6 mg

[a] Patients may remain on a lower dose for longer than one week or switch between doses (higher or lower) based on Investigator assessment of tolerability during the Titration Period.
[b] In the Long-Term Dosing Period, patients will continue to receive pitolisant up to 35.6 mg once daily in the morning upon wakening. Pitolisant dose may be adjusted (higher or lower) during the Long-Term Dosing Period (range: 8.9 mg to 35.6 mg) based on Investigator assessment of safety/tolerability and effectiveness. Pitolisant will be provided as 4.45 mg and 17.8 mg tablets. Pitolisant will be administered orally as a single dose once daily in the morning upon wakening.

Every effort should be made to educate patients on the importance of remaining compliant with study drug dosing. If a dose is missed during the study, the patient should take the next dose the following morning upon wakening.

3.6 Study Procedures and Flowchart

Details of the study procedures are provided in study HBS-101-CL-011 Protocol Section 7.

An overall schema of the study design is provided in study HBS-101-CL-011 Protocol Figure 1.

4 ENDPOINTS

4.1 Effectiveness Endpoints

The effectiveness endpoints are the Change from Baseline (EOT Visit/Visit 5 in study HBS-101-CL-010) in:

- Epworth Sleepiness Scale (ESS)
- Idiopathic Hypersomnia Severity Scale (IHSS)
- Clinical Global Impression of Severity (CGI-S) for IH
- Patient Global Impression of Severity (PGI-S) for Excessive Daytime Sleepiness (EDS)
- Functional Outcomes of Sleep Questionnaire 10 Item Version (FOSQ-10)
- Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment (PROMIS-SRI)
- Sleep Inertia Questionnaire (SIQ)

4.2 Safety Endpoints

The long-term safety and tolerability endpoints are:

- Incidence of adverse events (AEs)

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- Changes from Baseline (EOT Visit/Visit 5 in study HBS-101-CL-010) in clinical laboratory test results
- Changes from Baseline (EOT Visit/Visit 5 in study HBS-101-CL-010) in vital signs
- Changes from Baseline (EOT Visit/Visit 5 in study HBS-101-CL-010) in 12-lead electrocardiogram (ECG) results
- Changes from Baseline (EOT Visit/Visit 5 in study HBS-101-CL-010) in Columbia-Suicide Severity Rating Scale (C-SSRS) assessments

5 ANALYSIS POPULATIONS

5.1 Safety Population

The Safety Population will include all patients who are enrolled and take at least one dose of open-label pitolisant in study HBS-101-CL-011. All analyses will be performed on the Safety Population.

5.2 Eligible Population

The Eligible Population will include all patients who completed study HBS-101-CL-010. The Eligible Population will be used for the disposition summary.

6 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1 General Methods

All summaries will be presented by the treatment received (pitolisant or placebo) in the Double-Blind Randomized Withdrawal Phase of study HBS-101-CL-010 and overall (i.e., all patients in study HBS-101-CL-011). Baseline will be defined as the EOT Visit/Visit 5 from study HBS-101-CL-010. Changes (or shifts) from Baseline will be presented relative to the EOT Visit/Visit 5 from study HBS-101-CL-010.

Summary statistics (mean, standard deviation [SD], median, minimum, and maximum) will be reported for continuous variables and for changes from Baseline.

Unless otherwise specified, percentages will be calculated using the Safety Population as the denominator. In other instances, percentages will be determined using the number of patients with an observed value at the visit.

All analyses will be performed using SAS® version 9.4 or higher, unless otherwise specified.

All patient data will be included in listings. Patients with data entered into the database will be included in patient data listings in the appropriate analysis population.

6.2 Key Definitions

6.2.1 Study Baseline

The study Baseline is defined as the EOT Visit/Visit 5 from study HBS-101-CL-010. The EOT Visit/Visit 5 assessments from study HBS-101-CL-010 are the most recent assessments prior to the first dose of open-label pitolisant in this study. If a record is not available from EOT Visit/Visit 5 from study HBS-101-CL-010, the last record from study HBS-101-CL-010 will be used.

6.2.2 Study Day

Study day is calculated as:

- Date of event – reference date + 1, if the date of the event occurs on or after the reference date
- Date of event – reference date if the date of the event occurs prior to the reference date.

The reference date for study day is the date of first intake of pitolisant in study HBS-101-CL-011, which will be Study Day 1.

6.3 Missing Data

Every effort will be made to retain patients in the study; however, patients are free to withdraw from the study at any time for any reason. Patients who withdraw early will be asked to return to the clinic for an early termination visit for completion of assessments. Missing data (other than the imputation of partial dates for safety reporting described in Section 8.1) will not be imputed.

6.4 Multiple Comparisons

Multiple comparisons are not applicable for this study.

7 DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1 Patient Disposition and Withdrawals

Disposition data will be summarized as.

- The number of patients who completed the EOT/Visit 5 from study HBS-101-CL-010
- The number of patients who completed the EOT/Visit 5 from study HBS-101-CL-010 and did not enroll in study HBS-101-CL-011
- The number of patients who consented to participate in study HBS-101-CL-011
- The number of patients in the Safety Population in study HBS-101-CL-011
- The number and percentage of patients who discontinued treatment (including reasons for treatment discontinuation)
- The number and percentage of patients ongoing on treatment
- The number and percentage of patients who completed, discontinued, or are ongoing in study HBS-101-CL-011 including reasons for study discontinuation

For the items described, all percentages will be calculated using the number of patients in the Safety Population as the denominator. In addition, a figure summarizing disposition (i.e., consort diagram) will be prepared.

7.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, sex, child-bearing potential (females only), race, ethnicity, and baseline disorder characteristics will be reported for the Safety Population. Baseline disorder characteristics include time since IH diagnosis to the first dose in study HBS-101-CL-011 and

whether IH is with or without long sleep. Characteristics not collected in study HBS-101-CL-011 will be carried forward from study HBS-101-CL-010.

7.3 Medical History

For medical history, a summary table of the number and percentage of patients by system organ class (SOC) and preferred term (PT) will be produced for patients in the Safety Population. Medical history will be sorted by frequency by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, version 27.0 or later. For the summary tables, each patient is counted once under each SOC and PT category. A patient may be counted more than once if they have more than one medical history event coded under different SOC or PT categories. However, the patient will be counted only once in the overall category.

All medical history data will be listed.

7.4 Medications

Prior medications in the patient's medical record (including any medications taken during study HBS-101-CL-010) and prior and concomitant medications reported by the patient will be collected. Medications include prescription and over the counter medications (including herbal products and vitamins). Medications will be recorded between the signing of informed consent for study HBS-101-CL-011 to 30 days after the last dose in the study. Changes in concomitant medication use will be recorded in the electronic case report form (eCRF).

Medications will be classified as starting prior to first dose in study HBS-101-CL-010, starting prior to first dose in study HBS-101-CL-011 but after first dose of study HBS-101-CL-010, or starting concomitantly in study HBS-101-CL-011. A medication may be classified as used in more than one of these time periods.

Medications starting more than 30 days after the last dose of study drug will not be considered as concomitant.

Partial dates will be considered when determining if a medication is prior or concomitant. If the partial start or end dates are not sufficient to determine if the medication is prior, it will not be considered prior. If the partial start or end dates are not sufficient to determine if the medication is concomitant, it will be considered concomitant.

All prior and concomitant medications will be classified using the anatomical therapeutic chemical (ATC) classification coded terms and preferred drug names from the World Health Organization Drug Dictionary (WHODD), version Global B3 Mar2024 or later.

Summaries of prior and concomitant medications will be presented separately in tabular form using the level 4 ATC term as an upper classification level and the preferred drug name as a lower classification level. All medications will be summarized and sorted by most frequently reported by level 4 ATC term and preferred drug name within a given level 4 ATC term. The summary will consist of the frequency and percentage of patients in the Safety Population.

For each patient, the medication will be counted only once within a level 4 ATC term and only once under a given preferred drug name. A patient may appear more than once if they have more than one concomitant medication coded under different ATC terms or preferred drug names; however, the patient will be counted only once in the overall category.

All prior and concomitant medications will be listed.

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Concomitant medications of special interest, as identified by the Sponsor, may be summarized.

7.5 Concomitant Procedures

Concomitant procedures are nonpharmacologic therapies and procedures undergone by patients between the signing of informed consent for study HBS-101-CL-011 to 30 days after the last dose in the study. Concomitant procedures and changes in concomitant procedures will be recorded in the eCRF Concomitant procedures will be listed for the Safety Population.

7.6 Extent of Exposure

The duration of study drug exposure during the entire study will be summarized. The dosage in use at the start of the Long-Term Dosing Period will be summarized descriptively. Number and percentage of patients reaching at least 3 months, 6 months, 12 months, 18 months, and 24 months of exposure will be presented. Exposure will be summarized for the Safety Population.

Duration of Exposure = date of last dose in study – date of first dose in study + 1

Total duration of pitolisant exposure in HBS-101-CL-011 will be listed.

7.7 Treatment Compliance

Treatment compliance for the entire study will be summarized for the Safety Population. Number and percentage of patients will be presented for treatment compliance categories of <80%, ≥80 to ≤120%, and >120%.

Treatment compliance% = 100*(mg taken) / (mg expected)

mg taken = (4.45 mg × the number of tablets taken at that dose during the study + 17.8 mg × the number of tablets taken at that dose during the study) (i.e., sum of the mg dispensed minus the sum of the mg returned)

mg expected = assigned dose level times the number of days at that dose for each dose level from first dose to last assessment [date of last assessment in study – date of first dose in study + 1]

Treatment compliance data will be listed.

7.8 Protocol Deviations

Major protocol deviations will be summarized. All deviations will be listed.

8 EFFECTIVENESS

As specified in Section 4.1, the effectiveness endpoints are the Change from Baseline (EOT Visit/Visit 5 in study HBS-101-CL-010) in:

- ESS
- IHSS
  In addition to calculating the total score, the following IHSS subscale scores will be calculated:
  - Subscale 1: Daytime Functioning = sum of items 5, 9, 10, 11, 12, 13, 14

  - Subscale 2: Long Sleep Duration and Sleep Inertia = sum of items 1, 2, 3, 4, 8
  - Subscale 3: Napping = sum of items 6 and 7
- CGI-S for IH
  - Responses to the CGI-S will be mapped as 1 = None, 2 = Mild, 3 = Moderate, 4 = Severe, and 5 = Very Severe.
- PGI-S for EDS
  - Responses to the PGI-S will be mapped as 1 = None, 2 = Mild, 3 = Moderate, 4 = Severe, and 5 = Very Severe.
- FOSQ-10
  In addition to calculating the total score, the following FOSQ-10 subscales scores will be calculated, using non-responses only:
  - Subscale 1: Activity Level = mean of items 6, 8, 9
  - Subscale 2: Vigilance = mean of items 3, 4, 7
  - Subscale 3: Intimacy and Sexual Relationships = item 10
  - Subscale 4: General Productivity = mean of items 1, 2
  - Subscale 5: Social Outcomes = item 5

  Total FOSQ-10 score will be calculated as 5* mean of subscales 1 through 5
- PROMIS-SRI
- SIQ
  In addition to calculating the total score, the following SIQ subscale scores will be calculated:
  - Physiological: sum of items 4, 5, 7, 8, 9, 10, 11, 12
  - Responses to Sleep Inertia: sum of items 1, 2, 3, 6, 15
  - Cognitive: sum of items 16, 17, 18, 19, 21
  - Emotional: sums of items 13, 14, 20

Summary statistics will be reported for all continuous effectiveness study assessments at all time points (i.e., mean, SD, median, minimum, maximum). Both the raw assessment values and changes from Baseline (where applicable) will be summarized. Response to individual items will be listed. Mean ESS scores and mean change from Baseline will be plotted over time. Mean Change from Baseline will be plotted over time for IHSS, FOSQ-10, PROMIS-SRI and SIQ scores. Histograms of change from Baseline will be presented for CGI-S for IH and for PGI-S for EDS.

9 SAFETY

The Safety Population will be used for the safety analyses. All safety data will be listed and summarized. No formal inferential statistics will be performed for the safety analyses.

Safety data will be summarized from the date of the first dose of open-label pitolisant in study HBS-101-CL-011 and through 30 days after final dose of study drug.

9.1 Adverse Events

AEs that start during or after the first administration of study drug in study HBS-101-CL-011 up to 30 days after final dose of study drug in study HBS-101-CL-011, or AEs with an onset prior to first dose of study drug that worsen after first dose of study drug will be considered treatment-emergent adverse events (TEAEs).

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All TEAEs will be coded using MedDRA and tabulated by SOC and PT. MedDRA version will be specified in the table footers. For summaries by SOC and PT, a patient will be counted only once for each SOC and for each PT. Summaries by SOC and PT will be ordered by overall descending frequency of SOCs and then, within an SOC, by overall descending frequency of PTs.

For summaries by SOC, PT, and maximum severity, a patient is counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level. AEs with missing severity will be considered severe when determining highest severity level and for presentation in summary tables.

An AE is summarized as treatment-related if it is classified as definitely related, probably related, or possibly related in the eCRF by the Investigator. Adverse events with missing relationship to study drug will be considered treatment-related for summary tables.

The following summaries of TEAEs will be produced:

- An overall summary of the number and percentage of patients reporting at least 1 TEAE, at least 1 serious TEAE, at least 1 treatment-related TEAE, at least 1 treatment-related serious TEAE, at least 1 severe TEAE, at least 1 treatment-related severe TEAE, at least 1 TEAE leading to discontinuation of study treatment, at least 1 TEAE leading to study withdrawal, at least 1 treatment-related TEAE leading to discontinuation of study treatment, and at least 1 TEAE leading to death.
- TEAEs, overall and by SOC and PT
- Treatment-related TEAEs overall and by SOC and PT
- TEAEs by maximum intensity, overall and by SOC and PT
- Serious TEAEs, overall and by SOC and PT
- Nonserious TEAEs, overall and by SOC and PT
- TEAEs leading to discontinuation of study treatment, overall and by SOC and PT
- TEAEs leading to study withdrawal, overall and by SOC and PT
- Treatment-related TEAEs leading to discontinuation of study treatment, overall and by SOC and PT
- Treatment-related serious TEAEs, overall and by SOC and PT

All AEs will be listed. Serious AEs, AEs leading to discontinuation of study treatment, AEs leading to study withdrawal, and deaths will be listed separately. AEs will be flagged in the listings to identify treatment-emergent or not treatment-emergent.

In the event of a partial start date for an AE, the following imputation rules will be used solely to determine whether the AE is a TEAE. In listings, only actual dates will be included.

- If only the day is missing (month and day are present)
    - Month and year are the same as the month and year of the first dose of study drug
        - Impute missing start date as the date of the first dose of study drug in HBS-101-CL-011; AE will be considered treatment emergent.
    - Month and year are not the same as the month and year of the first dose of study drug in HBS-101-CL-011

        - Day will be imputed to the first of the month.
- If the month is missing, but the year is present
    - Year is the same as the year of the first dose of study drug in HBS-101-CL-011
        - Impute missing start date as the date of the first dose of study drug in HBS-101-CL-011; AE will be considered treatment emergent.
    - Year is not the same as the year of the first dose of study drug in HBS-101-CL-011
        - Impute missing month as January and missing day as the 1st of the month.
- If the year is missing
    - Impute any missing elements to the corresponding element in the date of the first dose of study drug in HBS-101-CL-011. If entire date is missing, impute missing start date as the date of the first dose of study drug in HBS-101-CL-011; AE will be considered treatment emergent.

- In any of the above cases, if the imputed start date is imputed as a date that is after the end date, then the imputed date will be changed to coincide with the end date of the AE.

9.2 Laboratory Evaluations

Clinical laboratory parameters (Table 2), with the exception of urine drug screen and pregnancy test, will be summarized. Urine drug screen and pregnancy test results will be listed only. For each laboratory test, individual patient values will be listed and values outside of the standard reference range will be flagged. Shift tables will be produced showing the frequency of shifts from Baseline (EOT Visit/Visit 5 of study HBS-101-CL-010) to the lowest and to the highest on study value in and out of the normal range as well as by visit.

To aid in the identification of potential Hy's Law cases, the following 3 lab parameter criteria will be programmed and presented in
a listing.

1) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of >3 x the upper limit of normal (ULN)
2) Total bilirubin (TBL) elevation of >2 x ULN
3) Alkaline phosphatase (ALP) <2 x ULN or is missing

Table 2: Clinical Laboratory Tests

Drug Screen (Urine) -Barbiturates -Cocaine metabolites -Opiates -Tetrahydrocannabinol -Phencyclidine -Methadone -Amphetamines/Stimulants -Hypnotics **Urinalysis** -Specific gravity -pH -Blood -Glucose -Protein -Leukocyte esterase -Ketones -Bilirubin -Nitrites -Casts -Crystals -Erythrocytes -Renal tubular epithelial cells -WBCs -Bacteria **Pregnancy Screen (FCBP only)** -Serum (at Screening only) -Urine (as scheduled after screening)	**Serum Chemistry** -Albumin -Alkaline phosphatase -Alanine aminotransferase -Aspartate aminotransferase -Blood urea nitrogen -Calcium -Chloride -Creatinine -Creatine kinase -Glucose -High-density lipoprotein -Low-density lipoprotein -Magnesium -Phosphorus -Potassium -Sodium -Total bilirubin -Direct bilirubin -Total cholesterol -Total protein -Triglycerides -Uric acid **Hematology** -Complete blood count, including platelet count and WBC count with differential -Hemoglobin -Hematocrit -HbA1C

FCBP = female of childbearing potential; HbA1C = hemoglobin A1C; WBC = white blood cell

9.3 Vital Signs

The change from Baseline (EOT Visit/Visit 5 of study HBS-101-CL-010) to each visit for vital sign variables (including body weight) will be summarized. Abnormal vital sign values, as identified by the site and collected on the eCRF, will be flagged and listed. Counts and percentages of patients with potentially clinically significant vital signs meeting the below criteria will be summarized.

- Heart rate (beats/min)
    - <60 bpm and decrease >15 bpm from Baseline
    - >100 bpm and increase >15 bpm from Baseline
- Systolic blood pressure (mmHg)
    - <90 mmHg and decrease >20 mmHg from Baseline

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  - >140 mmHg and increase >20 mmHg from Baseline

- Diastolic blood pressure (mmHg)
  - <50 mmHg and decrease >10 mmHg from Baseline
  - >100 mmHg and increase >10 mmHg from Baseline
- Weight (kg)
  - increase ≥10% from Baseline
  - decrease ≥10% from Baseline

9.4 12-Lead Electrocardiogram

Two sets of QTcF values and two QTcB values will be provided in listings:

- Site-provided QTcF/QTcB: values that were entered in eCRF by the site, which were either calculated by the ECG machine or by the site.
- Derived QTcF/QTcB: Values that were programmatically derived (using the standard formulas for QTcF and QTcB) based on RR and QT values entered in eCRF by the site.

Changes from Baseline (EOT Visit/Visit 5 of study HBS-101-CL-010) in ECG results (heart rate and PR, RR, QRS, QT, derived QTcF, and derived QTcB intervals) will be summarized. Categorical summaries based on derived QTcF will be provided to show changes from Baseline in derived QTcF >60 msec, and derived QTcF values >450 msec for male patients and >470 msec for female patients, as well as derived QTcF >500 msec regardless of gender.

For all ECG parameters, individual patient values will be listed (both derived and site-provided) and the QTcF categories will be flagged.

9.5 Physical Examination

Physical examination results will be listed.

9.6 Columbia-Suicide Severity Rating Scale

Results of the C-SSRS will be listed. A separate listing will be provided for all patients who answered "yes" to at least one question.

10 CHANGES FROM ANALYSES PLANNED IN PROTOCOL

There are no changes from the analyses planned in the study HBS-101-CL-011 protocol.

11 PROGRAMMING CONSIDERATIONS

11.1 General Considerations

- One SAS program can create several outputs.
- One output file can contain several outputs, or each output will be stored in a separate file.
- Output files will be delivered in Word format (.doc and .docx), portable document format (pdf), and Rich Text Format (.rtf).
- Numbering of TFLs will follow International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH E3) guidance.

11.2 Table, Figure, and Listing Format

11.2.1 General

- All TFLs will be produced in landscape format on American letter size unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.
- Tables will include listing source in footer. Listings will include dataset source in footer.

11.2.2 Headers

- All output will have the following header at the top left of each page:

Harmony Biosciences
Pitolisant (HBS-101-CL-011) XXXX
Data Cutoff Date: DDMMMYYYY

- Where XXXX will state the intent of use for each output (i.e., DSUR, CSR, etc.)
- Draft/Final Run <date>
- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table).
- The date the output was generated will appear along with the program name as a footer on each page.

11.2.3 Display Titles

- Each TFL will be identified by the designation and a numeral (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Safety Population)

11.2.4 Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of effectiveness tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, ‘unit’ will be included in the column or row heading, when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be placebo first for placebo-controlled studies and active comparators first for active comparator trials, followed by a total column (if applicable).

This document is confidential.

11.2.5 Body of the Data Display

11.2.5.1 General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

11.2.5.2 Table Conventions

- Units will be included where available
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented; therefore, counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
SD	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: '0.xxxx', where xxxx is the value rounded to 4 decimal places. If the p-value is less than 0.0001, then it is presented as <0.0001. If the p-value is returned as >0.9999, then it is presented as >0.9999.

- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). If a value rounds down to 0.0, then it will be displayed as '<0.1'. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC code), and AEs (by PT) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values that cannot be estimated will be reported as '-'

- The percentage of patients will normally be calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, which is usually the relevant number of patients exposed. Details will be described in footnotes or programming notes, as necessary.

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, a footnote or programming note will be added describing whether the patient is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria.

- Where a category with a subheading (such as SOC) needs to be split over more than one page, the subheading will be followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

11.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.

- Missing data will be represented on patient listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate.

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient will be output as 'N/A', unless otherwise specified.

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available.

11.2.5.4 Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean Change from Baseline) values will be displayed on the Y-axis.

11.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible.
- Patient specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program: myprogram.sas Listing source: 16.x.y.z').
- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed.
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

12 QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs Standard Operating Procedure (SOP) (3907).

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency, and commenting, and by review of the output produced.

This document is confidential.