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Statistical Analysis Plan

Sponsor	Incyte Corporation
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Document History

Version	Description/Changes
1.0	Initial Version

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List of Tables/Listings

List of Abbreviations

Abbreviation	Definition
AD	Atopic Dermatitis
AE	Adverse Event
AESI	Adverse Events Special Interest
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
COVID-19	Coronavirus Disease 19
CRF	Case Report Form
CSR	Clinical Study Report
eDiary	Electronic Diary
EMA	European Medicines Agency
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH	International Council for Harmonisation or Technical Requirements for Pharmaceutics for Human Use
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
NA	Not Applicable
PP	Per-Protocol
PROMIS	Patient-Reported Ouctomes Measurement Information System
REM	Rapid Eye Movement
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Sleep Efficiency
SOC	System Organ Class
SOL	Sleep Onset Latency
TEAE	Treatment-Emergent Adverse Event
TST	Total Sleep Time
V1	Visit 1/Day 1
V2	Visit 2/Week 4
V3	Visit 3/Week 8
WASO	Wake After Sleep Onset
WHO-DD	World Health Organization Drug Dictionary

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Incyte Corporation protocol number INCB 18424-902, an Open-Label, Single-Arm, Phase 4 Study of Ruxolitinib Cream in Adults with Atopic Dermatitis Experiencing Sleep Disturbance in the United States (Morpheus), dated 21JUN2022, Version 1.0. Reference materials for this statistical plan include the protocol and the accompanying data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (ICH, 1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (ASA, 2018) and the Royal Statistical Society (RSS, 2014), for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be approved before any inferential or descriptive analysis of data pertaining to study INCB 18424-902. This study was terminated early due to the sponsor's decision to cap enrollment at 47 participants because of enrollment challenges.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this Phase IV study is to evaluate the reduction in sleep disturbance after using ruxolitinib cream.

2.1.2. Secondary Objectives

The secondary objective is to further evaluate the reduction in sleep disturbance after using ruxolitinib cream.

2.1.3. Exploratory Objectives

The exploratory objectives of this study are:

- [redacted]
- [redacted]

- [redacted]
- [redacted]

2.2. Study Endpoints

2.2.1. Efficacy Endpoints

2.2.1.1. Primary Efficacy Endpoint

The estimand for the primary efficacy endpoint has the following components:

Attribute	Definition
Treatment	The treatment of interest is ruxolitinib cream.
Population	The population of interest is adults with active Atopic Dermatitis (AD) further defined by the inclusion and exclusion criteria.
Variable of Interest	The variable of interest is the mean change in Total Sleep Time (TST) as measured by the average change from Baseline to Week 8 by the Ōura Ring wearable device.
Intercurrent Events	Study discontinuation prior to the planned assessment timeframe.

2.2.1.2. Secondary Efficacy Endpoint

Secondary Objective	Secondary Efficacy Endpoint
To further evaluate the reduction in sleep disturbance after using ruxolitinib cream.	The estimand for the secondary efficacy endpoint of this study is change from baseline in PROMIS Sleep Disturbance – Short Form 8b score at Week 8.

2.2.1.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints of this study include the following:

Exploratory Objective	Exploratory Efficacy Endpoint
[redacted]	

	Ring wearable device at Week 8.
[redacted]	

2.2.2. Safety Endpoints

Study subjects will be assessed for the safety and tolerability of ruxolitinib cream throughout the study. Following completion of the treatment period (or the last application of study drug for those who discontinue early), participants will have follow-up assessments 30 (+7) days after the end of treatment to evaluate safety.

The safety endpoints of this study include the following:

- The type, frequency, and severity of treatment emergent AEs (TEAEs).
- Occurrence of serious AEs (SAEs).
- Vital signs
- Clinical laboratory assessments

2.2.3. Other Exploratory Endpoints

Exploratory Objective	**Exploratory Efficacy Endpoint**
[redacted]	

3. Overall Study Design and Plan

3.1. Overall Design

This is a Phase 4, multicenter, open-label, single-arm study to evaluate the reduction in sleep disturbance among participants with AD after treatment with ruxolitinib 1.5% cream. Ruxolitinib cream is a topical formulation of ruxolitinib phosphate, an investigational product that has been developed for the treatment of inflammatory diseases of the skin.

This study will enroll approximately 100 adults (≥18 years of age) with at least mild severity AD who have sleep disturbance. Individuals with known sleep-related conditions that are not associated with their AD diagnosis will be excluded from the study.

A minimally invasive wearable device (Ōura Ring) and a [redacted] will be used to collect objective measures of sleep during the study. The Oura Ring will be used during the screening sleep assessment to determine study eligibility as well as during a 7-day pretreatment sleep assessment to further determine eligibility and to establish baseline sleep patterns. See Appendix A for Total Sleep Time (TST) eligibility calculations. The two technologies will also be applied throughout the 8-week treatment period to monitor postbaseline sleep patterns.

Following completion of the treatment period (or the last application of study drug for those who discontinue early), participants will have follow-up assessments 30 (+7) days after the end of treatment to evaluate safety.

Throughout the study, participants will complete the following patient reported outcomes (PROs) using their eDiary: Itch NRS (daily), PROMIS Sleep Disturbance – Short Form 8b (daily), and PROMIS Sleep-Related Impairment – Short Form 8a (weekly).

3.2. Sample Size and Power

All participants will receive treatment with ruxolitinib cream 1.5% twice a day. The primary analysis will compare the difference in TST between baseline and Week 8. If the true increase in TST is 30 minutes, a sample size of 70 participants will provide > 90% power to reject the null hypothesis at $\alpha = 0.05$. Accounting for loss to follow-up and device malfunction, a total of 100 participants are planned to be enrolled into the study. [Note: due to enrollment challenges, 47 participants were enrolled.]

3.3. Study Population

The study population comprise male and female adults (≥ 18 years of age) with a diagnosis of AD for at least 2 years, BSA involvement of 3% to 20% (excluding scalp), an IGA score ≥ 2, Itch NRS ≥ 4, PROMIS Sleep Disturbance – Short Form 8b score ≥ 21, average Total Sleep Time/night ≤ 6.5 hours, and no underlying sleep disorders.

3.4. Treatments Administered

All study subjects will apply ruxolitinib cream at the FDA-approved strength (1.5%) twice a day over the 8-week treatment period, during which participants will treat all baseline AD lesions twice a day, regardless of whether or not the lesion(s) improve. New and/or expanded areas of AD may also be treated but not in excess of a total of 20% BSA (for original plus new areas) per application.

All participants will have follow-up assessments 30 (+7) days after the end of treatment duration [Week 8/End of Treatment (EOT) or Early Termination (ET)] to evaluate safety. Figure 1 below presents the study schema.

[a] BSA of 3 to 20% excluding AD area(s) on the scalp.

[b] PROMIS Sleep Disturbance – Short Form 8b questionnaire.

[c] As measured by Ōura Ring wearable device during the screening sleep assessment (which is separate from the pretreatment sleep assessment).

[d] Washout current medication for AD and any other excluded treatments.

[g] Clinical assessments completed at Day 1, Week 4, and Week 8.

[h] Continuous treatment with ruxolitinib cream 1.5% twice a day of all areas identified at baseline, regardless of lesion clearance; new and/or expanded areas of AD may also be treated but not in excess of a total of 20% BSA.

3.5. Method of Assigning Subjects to Treatment Groups

This is an open-label study.

3.6. Blinding and Unblinding

This is an open-label study.

3.7. Schedule of Events

Please see protocol INCB 18424-902, An Open-Label, Single-Arm, Phase 4 Study of Ruxolitinib Cream in Adults with Atopic Dermatitis Experiencing Sleep Disturbance in the United States

(Morpheus) for a detailed schedule of events.

4. Statistical Analysis and Reporting

The final study analysis will be conducted only after all subjects have completed the study as described in the referenced protocol, a thorough review of all collected data has been conducted and approved, and a final SAP has been approved and signed prior to locking of the final data.

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will primarily use SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each visit. Percentages will be presented to 1 decimal place. Counts of zero will be presented without percentages.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level usin 2-tailed tests, and *p* values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests. All *p* values will be displayed in four decimals and rounded using standard scientific notation (e.g. 0.XXXX). If a *p* value less than 0.0001 occurs it will be shown in tales as <0.0001; similarly, if a *p* value greater than 0.9999 occurs, it will be shown in tables as >0.9999. Confidence intervals will be reported to 1 degree of precision more than the observed data.

4.2. Interim Analysis and Data Monitoring

No interim analyses or data monitoring are planned.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Intent-To-Treat Population (ITT):** The ITT population includes all subjects who enrolled in the study.

- **Safety Population (SAF):** The Safety Population includes all subjects who received at least 1 application of study drug during the treatment period.
- **Per Protocol (PP)**: The PP Population includes all subjects who have no important protocol deviations.

Assignment of subjects to populations will be confirmed at a data review to be held before the study database is locked.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

For the following endpoint variables, calculations of change from baseline to Week 8 in sleep data, baseline comprises the 7-day average prior to the first dose: TST, [redacted], PROMIS 8b. See Section 6.1.7 for details.

Otherwise, for non-sleep data, the last observation recorded on or before the first dose of treatment will be used as the baseline value.

6.1.2. Adjustments for Covariates

There will be no adjustments for covariates in any of the analyses.

6.1.3. Multiple Comparisons

For the primary efficacy endpoint, differences will be assessed at alpha = 0.05. No adjustments will be made for multiple comparisons for other secondary/exporatory endpoints.

6.1.4. Handling of Dropouts or Missing Data

See Section 6.1.7 for details regarding missing PROMIS score and 6.1.8 for details regarding missing AE date data handling conventions.

6.1.5. Analysis Visit Windows

For all analyses, early termination and unscheduled visits will be assigned analysis visits according to the analysis windows in the following table. Where multiple measurements for a particular parameter appear within an analysis window, the result closest to the target day will be used. If equidistant, the latter result will be used for the summary measure. Though all measures may not be used in the data summaries, all measurements appear in the datasets and listings.

Scheduled Visit (Subject Visit Window)	Analysis Visit	Analysis Window Target Day	Analysis Window	
			Lower Bound	Upper Bound
Screening	Screening	NA		
Enrollment	Day 1	1		1

(Day 1)				
Visit 2 (Week 4 ± 7 days)	Week 4	28	2	55
Visit 3 (Week 8 + 7 days)	Week 8	56	56	63
Follow-Up (30 Days Post Visit 3 + 7 days)	Follow-Up	86	64	NA

6.1.6. Pooling of Sites

No pooling will be done.

6.1.7. Derived Variables

6.1.7.1. General

- **Age:** Age will be calculated as the integer difference in years between the subject's year of informed consent and the year of birth.
- **Change from baseline:** The value at the target time point minus the value at baseline.
- **Prior and concomitant medications:** All medications taken prior to Screening or in the time interval between Screening and Enrollment/Visit 1 will be considered prior medications, whether or not they were stopped before Enrollment/Visit 1. Any medications continuing or starting after Enrollment/Baseline Visit will be considered concomitant. If a medication starts before enrollment and continues after enrollment it will be considered both prior and concomitant.
- **Study Day:** For analysis purposes, Study Day is calculated relative to the date of first dose of study drug. For study days on or after treatment start, study date = date – treatment start date + 1. For study days before treatment start, study day = date – treatment start date.
- **Treatment-emergent adverse event (TEAE):** Defined as 1) AEs with onset at the time of or following the start of treatment with IP through Week 8 (EOT) or 2) AEs starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through Week 8 (EOT).

6.1.7.2. Sleep Definitions

[redacted]

6.1.7.3. Total Sleep Time (TST)

- **Ōura Ring**
  For each days' worth of sleep data, the TST for the previous night will be calculated using sleep status reported between 6pm on the previous day through 9am that day. The wearable device data tracks bedtime start and bedtime end times for each of the patient's sleep epochs as well as calculates a total sleep time within that epoch. Any bedtime end that is after 6pm the night prior or bedtime start that is before 9am the day of will have that sleep epoch data row be included towards the total TST for that day. All epochs that meet criteria will have their total sleep duration (reported in seconds) summed and the TST for that day will be totaled and divided by 60 to get minutes. The 7 nights prior to Visit 1 will comprise the 7-day TST average for baseline, the 7 nights prior to Visit 2/Week 4 (V2) will comprise the 7-day TST average for V2, and the 7 nights prior to Visit 3/Week 8 will comprise the Week 8 average TST. Subjects must have >=4 nights worth of sleep data in order for the N-day average to be calculated where N is the number of non-missing TST days' worth of data to be included. See Section 13.4.1 for more details.

[redacted]

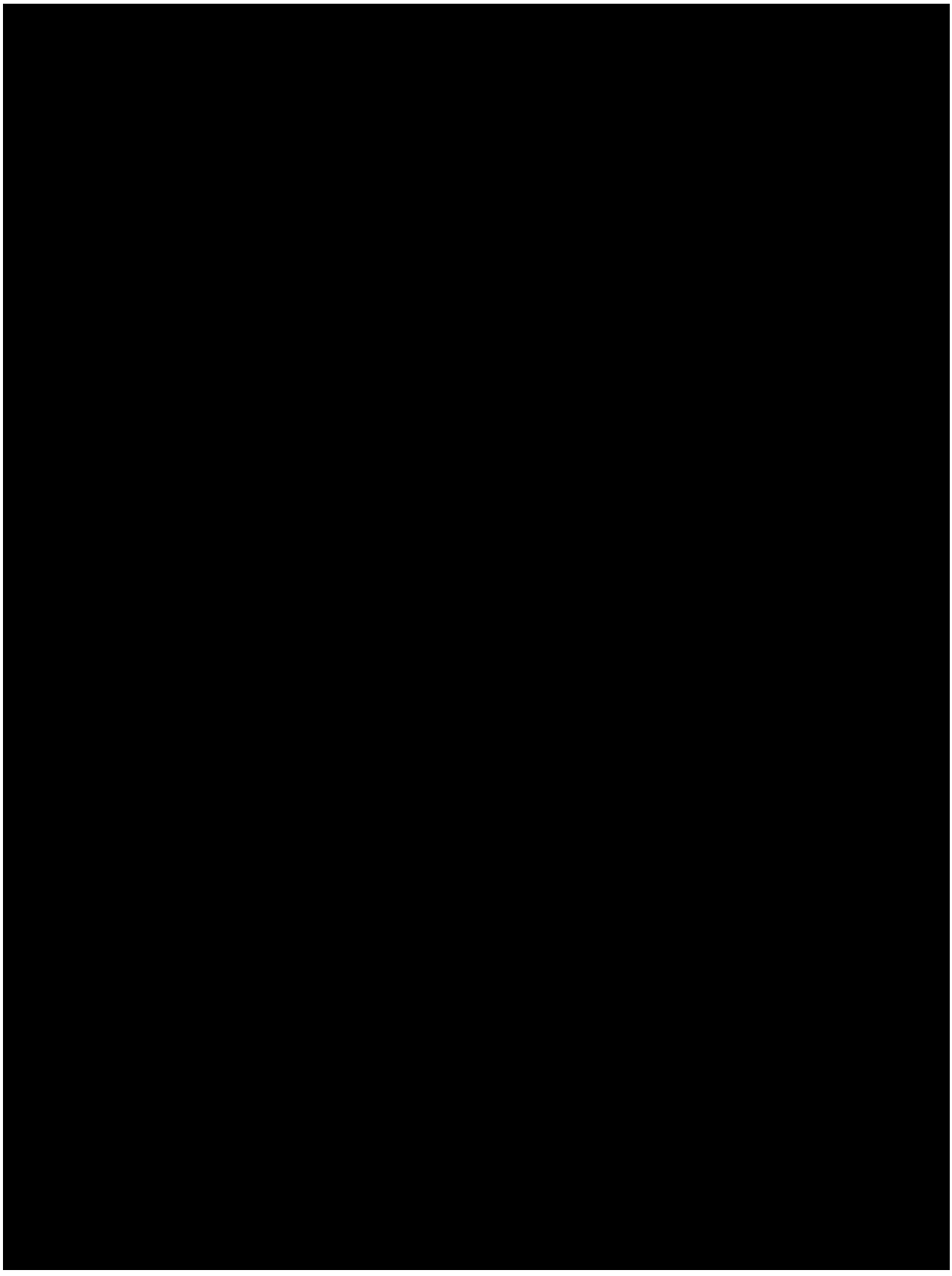
6.1.7.4. PROMIS 8a

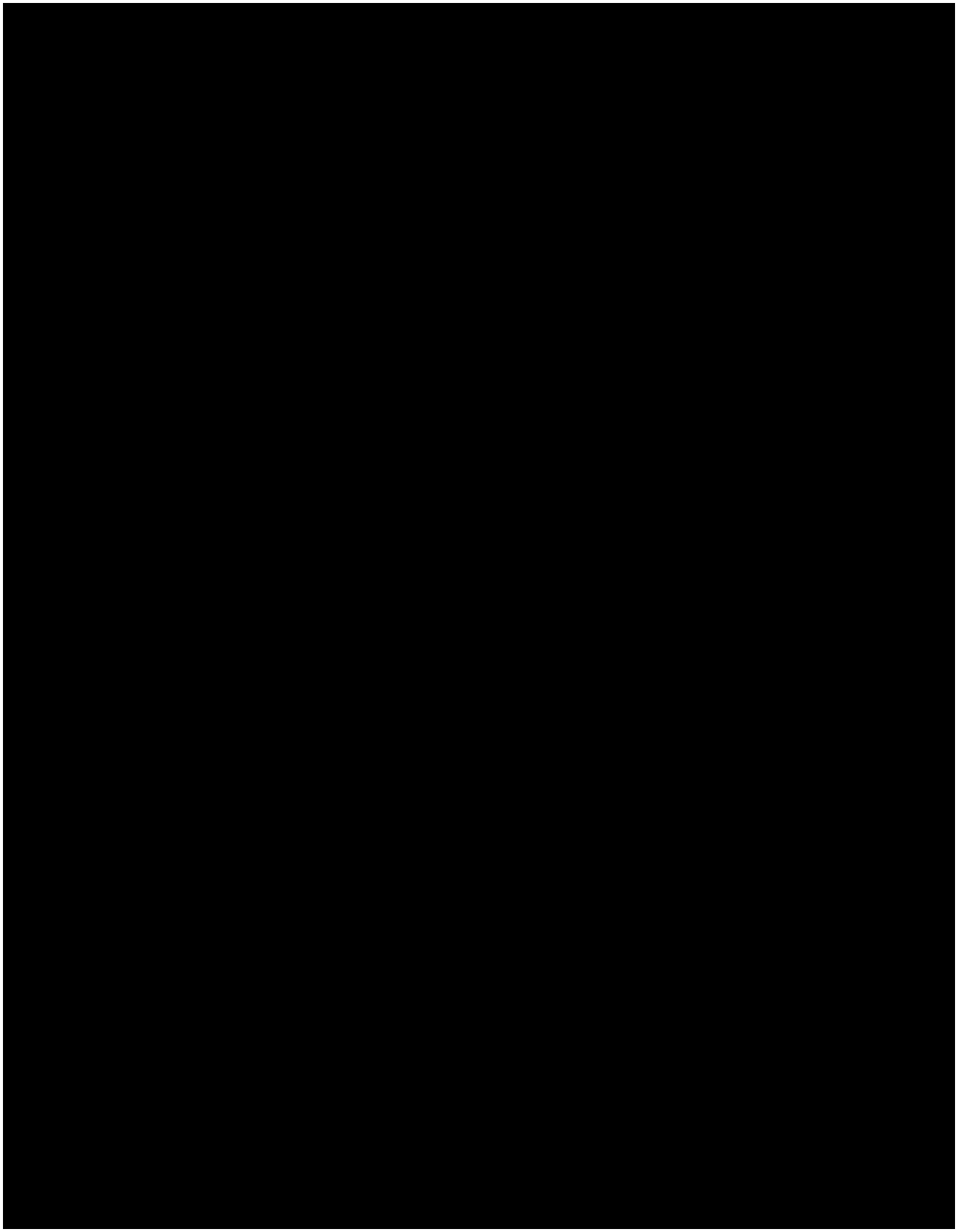
The PROMIS 8a form is a validated instrument used to measure the severity of sleep-related impairment. A higher PROMIS score indicates more severe sleep impairement. The PROMIS score includes 8 items and uses a 1-5 severity scale and is filled out weekly. The questionnaires are required to be filled out in their entirety in order to save.

The PROMIS total score will be calculated as the sum of the 8 items and will range from 8 to 40.

The baseline PROMIS 8a score will be the last score on or before Visit 1, the Visit 2/Week 4 score will be the last score on or before V2 within 7 days, and the Visit 3/Week 8 score will be the last score on or before V3 within 7 days.

[redacted]





6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *p* values will be displayed in four decimals and rounded using standard scientific notation (eg, 0.XXXX). If a *p* value less than 0.0001 occurs, it will be shown in tables as < 0.0001.

Adverse events will be coded using the MedDRA version 27.1 thesaurus.

A treatment related AE is any AE with a relationship to the study drug of possibly related.

If partial start dates occur for AEs, prior medications, or concomitant medications, the convention for replacing missing dates for the purpose of statistical analysis is as follows:

- If the year is missing do not impute
- If only the day is missing and the month and year match the first dose date and the end date is on or after the first dose date, then the day assigned is equal to the first dose date; if the month and/or year do not match the first dose date or the end date is prior to the first dose date, then the day is assigned 01.
- If only the month is missing and the day and year match the first dose date and the end date is on or after the first dose date, then the month assigned is equal to the first dose date; if the day and/or year do match the first dose date or the end date is prior to the first dose date, then the month assigned is JAN.
- If both the month and day are missing and the year matches the first dose date and the end date is on or after the first dose date, then the date assigned is the first dose date; if the year does not match the first dose date or the end is prior to the first dose date, then the day/month is assigned 01JAN.

Partial end dates will not be imputed.

7. Study Patients/Subjects and Demographics

7.1. Disposition of Patients/Subjects and Withdrawals

Disposition will include tabulations of the number of subjects who signed an ICF, the number of subjects who received treatment, tabulated reasons for discontinuation from the study, and number of subjects in each of the following analysis populations: ITT, SAF, and PP.

7.2. Protocol Violations and Deviations

Protocol deviations will be tracked, recorded, and reviewed prior to database lock, following the Protocol Deviation Guidance Plan for this study. The deviation list will be stored in Remarque and transferred to the biostatistics team for analysis.

Protocol deviations will be classified as “Important” or “Non-Important.” An important deviation poses a possible safety issue to the participant, or it has a potential impact on the statistical analysis of the clinical data. A non-important deviation is identified as any protocol deviation that does not meet the criteria for an important deviation. Recurrent non-important deviations may escalate to the level of important. See PDGP for details.

The final decision regarding classification of deviations and inclusion and exclusion of subjects from the analysis populations will be based on a final listing of protocol deviations. Subject inclusion/exclusion in analysis populations will be determined during a blinded review meeting before study data are unblinded. Clinical and Biostatistics team members will provide input to the decision and the final composition of the analysis populations will be approved by the Sponsor.

Protocol deviations will be summarized for the ITT population. Data will also be presented in a by-subject listing.

7.3. Demographics and Other Baseline Characteristics

For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

Summary statistics for demographic and other baseline characteristics will be presented overall. Demographic variables will include age, sex, race, ethnicity, height, weight, and body mass index (BMI). Baseline variables will include IGA, %BSA affected, and vital signs. Demographic and baseline characteristic data will be summarized for the ITT and PP populations.

Prior and concomitant medications will be classified by ATC Class Level 2 and preferred term (PT). The number and percentage of subjects taking each classification of medication will be summarized overall. The analysis will be conducted for the ITT population. Data will also be presented in a by-subject listing.

Medical history will be classified by system organ class (SOC) and PT. The number and percentage of subjects with each classification will be summarized overall. The analysis will be conducted for the ITT population. Data will also be presented in a by-subject listing.

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

The primary endpoint will be tested for the following hypothesis:

H_0: There is no difference in the mean TST between Baseline and Week 8 (from the Ōura Ring wearble device).

H_1: There is a difference in the mean TST between Baseline and Week 8 from the Ōura Ring wearable device).

The average total sleep will be summarized by visit using descriptive statistics. A two-sample paired t-test will be used to test a difference between the average sleep at baseline and Week 8. The mean pair-wise difference, 95% confidence interval of the difference, and *p* value will be presented. The primary analysis will be conducted on the PP population who also have both a baseline and Week 8 assessment available.

8.1.1. Sensitivity Analysis of the Primary Efficacy Endpoint

A sensitivity analysis will be performed on the primary efficacy endpoint to include those subjects with missing Week 8 sleep results. The sensitivity analysis on the difference in mean TST will be considered for the ITT population.

Missing average TST at Week 8 will be imputed utilizing a Last Observation Carried Forward (LOCF) approach. Because the Ōura Ring data is collected daily, needing at least 4 observations within 7 days to calculate a 7-day average, the last rolling 7-day average that can be calculated

within a subject's TST will be utilized as the observation to carry forward to Week 8.

Similarly to the primary analysis, the average sleep will be summarized at Baseline and the imputed Week 8 using descriptive statistics. The mean pair-wise difference, 95% confidence interval of the difference, and *p* value will be presented.

8.2. Secondary Efficacy Analysis

The secondary endpoint will be tested for the following hypothesis:

H_0: There is no difference in the mean PROMIS 8b total score between Baseline and Week 8.

H_1: There is a difference in the mean TPROMIS 8b total score between Baseline and Week 8.

The average total score will be summarized by visit using descriptive statistics. A two-sample paired t-test will be used to test a difference between the average score at baseline and Week 8 in the ITT population. The mean pair-wise difference, 95% confidence interval of the difference, and *p* value will be presented.

8.3. Exploratory Efficacy Analysis

No formal statistical testing will be performed on exploratory endpoints.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, changes in clinical laboratory values, changes in vital signs, and physical examinations of the affected areas.

All safety analyses will be performed on the Safety population (as defined in Section 5).

9.1. Adverse Events

Missing and partially missing start dates will be imputed for the purpose of analysis as described in Section 6.1.8.

All adverse events (AEs), treatment emergent adverse events (TEAEs), and serious adverse events (SAEs) will be coded using the MedDRA v. 27.1. Treatment Emergent AEs are defined in Section 6.1.7.1.

The number and percent of subjects reporting treatment emergent AEs, grouped by MedDRA SOC and PT, will be tabulated. In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each PT.

A summary table will be created summarizing the number and percent of subjects with the following:

- At least one TEAE
- At least one possibly related TEAE
- At least one serious TEAE
- At least one serious TEAE possibly related to Study Drug
- At least one TEAE leading to permanent treatment discontinuation
- At least one TEAE leading to Death
- At least one TEAE by maximum severity

In addition, the following TEAE data will be summarized for each MedDRA SOC and PT:

- Incidence of overall TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT, and Severity
- Incidence of Severe TEAE by SOC and PT
- Incidence of TEAEs by SOC, PT, and Relationship
- Incidence of Related TEAEs by SOC and PT
- Incidence of Serious TEAEs by SOC and PT
- Incidence of TEAEs leading to Study Discontinuation

In the summaries showing severity and relationship to study medication the event with the maximum severity (Life Threatening>Severe>Moderate>Mild) or relationship (Related/Not Related) will be reported. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = related).

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged. A listing of all AE data sorted by subject, including verbatim term, MedDRA SOC and PT, and all other information from the AE eCRF will be generated.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and preferred term will be prepared for the Safety Population. No inferential statistical tests will be performed.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed as well as tabulated by SOC and PT.

9.2. Clinical Laboratory Evaluations

Laboratory test results will be summarized descriptively by time point as both observed values and change from baseline values.

The number of subjects with clinical laboratory values below, within, or above the normal range by time point and in relation to baseline will be tabulated for each clinical laboratory analyte by treatment group (shift table).

Central Labs' normal ranges are provided from the Lab Vendor Q2 within the data transfer. Any local labs performed will utilize the local lab ranges input from the site into the EDC.

Lab Units will be standardized and displayed as follows:

Analyte Name	**Unit**
ALT	U/L
Albumin	g/L
Alkaline Phosphatase	U/L
AST	IU/L
Basophils	10^9/L
Basophils/Leukocytes	%
Bicarbonate	mmol/L
Direct Bilirubin	µmol/L
Total Bilirubin	µmol/L
Blood Urea Nitrogen	mmol/L
Calcium	mmol/L
Chloride	mmol/L
HCG	Positive/Negative
Creatinine	µmol/L
Eosinophils	10^9/L
Eosinophils/Leukocytes	%
Ery. Mean Corpuscular Volume	fL
Erythrocytes (RBC)	10^12/L
Erythrocytes Distribution Width (RDW)	%
FSH	IU/L
Glucose	mmol/L
HCT	Fraction of 1
HGB	g/L
HIV Screening	Reactive/Non-Reactive
Lactate Dehydrogenase	IU/L
Leukocytes (WBC)	10^9/L
Lymphocytes	10^9/L
Lymphocytes/Leukocytes	%
Mean Platelet Volume	fL

Monocytes	10^9/L
Monocytes/Leukocytes	%
Neutrophils	10^9/L
Neutrophils/Leukocytes	%
Phosphate	mmol/L
Platelets	10^9/L
Potassium	mmol/L
Protein	g/L
Sodium	mmol/L

Descriptive summaries of observed values and change from baseline will be presented for continuous hematology and chemistry for overall subjects at each study visit.

Laboratory values that are outside the normal range will be presented via a shift table and also be flagged in the data listings and presented with the corresponding normal ranges.

Serology tests including urinalysis, pregnancy, and HIV test results will be listed.

9.3. Vital Signs

Descriptive summaries of observed values and changes from baseline will be calculated for supine systolic blood pressure, supine diastolic blood pressure, heart rate, respiratory rate, and oral body temperature for overall subjects at each study visit.

9.4. Concomitant Medication

Prior and concomitant medications are defined in Section 6.1.7.1 and will be summarized descriptively using counts and percentages.

- Medications will be coded using WHODD v. MAR23B32.

9.5. Physical Exams

Whether physical exams were performed at visits will be listed.

10. Changes from Planned Analysis

- Inclusion of the ITT population
- Sponsor decision to cap enrollment at 47 subjects due to enrollment challenges.
- Exclusion of the Sufficiently Treated Population (STP) due to ePRO use challenges
- No formal statistical testing of the exploratory endpoints.

11. Other Planned Analysis

No additional are prospectively planned for this study.

11.1. Coronavirus COVID-19

The SARS-CoV-2 virus and variants may still be a threat and safety precautions may still be in place during study enrollment. To assess the impact of the COVID-19 pandemic on study procedures, study staff will complete the COVID-19 Impact questionnaire. Should a study visit be affected by COVID-19, study staff will record how the visit was affected (missed, abbreviated, delayed, performed remotely, or otherwise deviating from the planned format in the protocol) and which procedures were impacted. All COVID-19 protocol deviations will be noted in the deviation listing.

12. References

ASA. (2018) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2018. http://www.amstat.org/about/ethicalguidelines.cfm

ICH (1998). ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9; 1998. https://database.ich.org/sites/default/files/E9_Guideline.pdf

RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. https://rss.org.uk/about/policy-and-guidelines/code-of-conduct/.

13. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the the file name and path, and the source of the data (e.g. listing number).

The following are planned summary tables for protocol number INCB 18424-902. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

13.1. Demographic Data Summary Tables and Figures

Table 1: Demographic Data Summary Tables and Figures

Table Number	Population	Table Title/Summary
Table 14.1.1	All Subjects	Summary of Study Populations & Subject Disposition
Table 14.1.2	ITT	Summary of Important Protocol Deviations
Table 14.1.3.1	ITT	Summary of Demographics and Baseline Characteristics
Table 14.3.1.2	PP	Summary of Demographics and Baseline Characteristics
Table 14.1.4	ITT	Summary of Medical Health History

Table 14.1.5	ITT	Summary of Atopic Dermatitis and Sleep History
Table 14.1.6	ITT	Summary of Prior Medications by Therapeutic Class and Preferred Term
Table 14.1.7	ITT	Summary of Concomitant Medications by Therapeutic Class and Preferred Term

13.2. Efficacy Data

Table 2: Efficacy Data

Table Number	Population	Table Title / Summary
Table 14.2.1	PP	Summary of Mean TST Change from Baseline (Ōura Ring Data)
Table 14.2.1.1	ITT	Summary of Mean TST Change from Baseline (Ōura Ring Data) – Sensitivity Analysis
Table 14.2.2	ITT	Summary of PROMIS 8b Change from Baseline
Table 14.2.3	ITT	Summary of SOL Change from Baseline (Ōura Ring Data)
Table 14.2.4	ITT	Summary of WASO Change from Baseline (Ōura Ring Data)
Table 14.2.5	ITT	Summary of Sleep Efficiency Change from Baseline (Ōura Ring Data)
Table 14.2.6	ITT	Summary of PROMIS 8a Change from Baseline
Table 14.2.7	ITT	Summary of Itch NRS Change from Baseline
Table 14.2.8	ITT	Summary of %BSA Change from Baseline
Table 14.2.9	ITT	Summary of IGA Change from Baseline
Table 14.2.10	ITT	Summary of Light, Deep, REM (Ōura Ring Data)
[redacted]		

13.3. Safety Data

Table 3: Safety Data

Table Number	Population	Table Title / Summary
14.3.1 Displays of Adverse Events		
Table 14.3.1.1	Safety	Incidence of Overall Treatment-Emergent Adverse Events
Table 14.3.1.2	Safety	Incidence of Treatment-Emergent Adverse Events by SOC and PT
Table 14.3.1.3	Safety	Incidence of Treatment-Emergent Adverse Events by SOC, PT, and Severity

Table Number	Population	Table Title / Summary
Table 14.3.1.4	Safety	Incidence of Severe Treatment-Emergent Adverse Events by SOC and PT
Table 14.3.1.5	Safety	Incidence of Treatment-Emergent Adverse Events by SOC, PT, and Relationship
Table 14.3.1.6	Safety	Incidence of Related Treatment-Emergent Adverse Events by SOC and PT
14.3.2 Summary of Serious and Significant Adverse Events		
Table 14.3.2.1	Safety	Summary of Serious Treatment-Emergent Adverse Events by SOC and PT
Table 14.3.2.2	Safety	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation
14.3.3 Narratives of Deaths, Other Serious, and Certain Other Significant Adverse Events		
Table 14.3.3.1	Safety	Listing of Deaths
Table 14.3.3.2	Safety	Listing of Serious Adverse Events
Table 14.3.3.3	Safety	Listing of Treatment-Emergent Adverse Events Leading to Discontinuation
14.3.4 Abnormal Laboratory Values		
Table 14.3.4.1	Safety	Summary of Abnormal Laboratory Values
14.3.5 Laboratory Data Summary Tables		
Table 14.3.5.1	Safety	Summary of Clinical Chemistry
Table 14.3.5.2	Safety	Summary of Hematology
14.3.6 Other Safety Data Summary Tables		
Table 14.3.6.1	Safety	Summary of Vital Signs by Visit

13.4. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number INCB 18424-902.

In general, one listing will be produced per CRF domain. All listings will be sorted by site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (eg, repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 4: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2 Subject Data Listings		
16.2.1 Subject Discontinuations/Completions		
Listing 16.2.1.1	All subjects	Study Populations and Disposition
16.2.2 Protocol Deviations		
Listing 16.2.2.1	All subjects	Inclusion/Exclusion Criteria
Listing 16.2.2.2	ITT	Protocol Deviations
16.2.4 Demographic Data and Other Baseline Characteristics		
Listing 16.2.4.1	ITT	Demographics and Baseline Characteristics
Listing 16.2.4.2	ITT	Medical History
Listing 16.2.4.3	ITT	Atopic Dermatitis and Sleep History
Listing 16.2.4.4	ITT	Prior Medications
Listing 16.2.4.5	ITT	Concomitant Medications
16.2.5 Compliance and/or Drug Concentration Data		
Listing 16.2.5.1	Safety	Study Drug Accountability/Administration
16.2.6 Individual Efficacy Response Data		
Listing 16.2.6.1	ITT	Oura Results (TST, SOL, WASO, SE) Baseline and Week 8
Listing 16.2.6.2	ITT	Oura Epoch Results
Listing 16.2.6.3	ITT	PROMIS 8a
Listing 16.2.6.4	ITT	PROMIS 8b
Listing 16.2.6.5	ITT	Itch NRS
Listing 16.2.6.6	ITT	Listing of % BSA
Listing 16.2.6.7	ITT	Listing of IGA
[redacted]		
16.2.7 Adverse Event Listings		
Listing 16.2.7.1	Safety	Overall Adverse Events
Listing 16.2.7.2	Safety	Severe Adverse Events
Listing 16.2.7.3	Safety	Treatment-Related SAEs
16.2.8 Laboratory Values (by Patient/Subject)		
Listing 16.2.8.1	Safety	Hematology Laboratory Evaluations
Listing 16.2.8.2	Safety	Clinical Chemistry Laboratory Evaluations
Listing 16.2.8.3	Safety	Serology Test Results
Listing 16.2.8.4	Safety	Abnormal Laboratory Values
16.2.9 Other Clinical Observations and Measurements		

Data Listing Number	Population	Data Listing Title / Summary
16.2 Subject Data Listings		
Listing 16.2.9.1	Safety	Vital Signs Measurements
Listing 16.2.9.2	Safety	Physical Examinations

13.4.1. Appendix A: Total Sleep Time (TST) Study Eligibility

This appendix outlines how the average TST for both the Screening and Pretreatment periods are calculated in order to determine eligibility for the study. It additionally describes how subjects move from the Screening to the Pretreatment period and Pretreatment to Treatment.

Screening:

Upon completing the initial screening activities (signed ICF, requested labs, screening PROs), participants will receive wireless and wearable devices that will assess their sleep patterns. The data from the wearable device will be used for additional screening. The 7-day average TST will be calculated daily starting with the first 7-day time span of available sleep monitoring data and used to determine if the patient qualifies to move into the Pretreatment sleep assessment period. If at any time during the Screening period, the participant has an average 7-day TST $\leq$ 6.5 hours, then the participant will be flagged to be moved into the Pretreatment sleep assessment period once their washout (if applicable) has completed. A maximum of 35 days will be given in this Screening period to qualify for the Pretreatment phase. A subject needing more than 35 days in Screening must be rescreened into the study. If the participant does not have an average 7-day TST $\leq$ 6.5 hours during this 35-day period, then the participant is considered a screen failure.

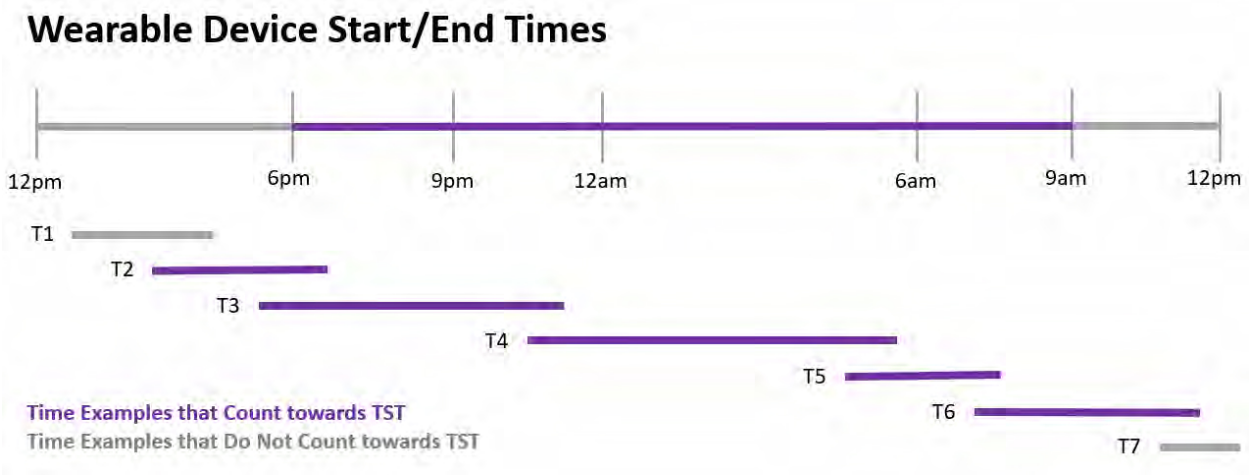
Calculation Specifics:

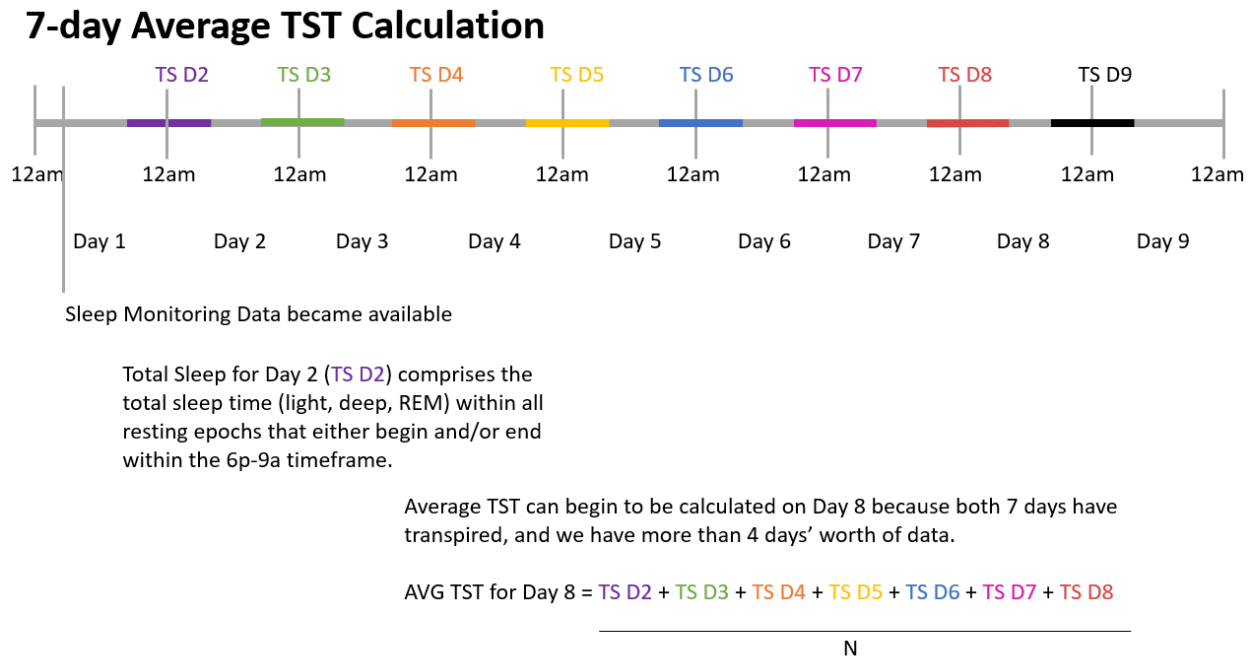
The TST rolling average must include $\geq$4 days' worth of data within a 7-day time span. If there is <4 days, an average will not be calculated and the average will resume when 4 or more days of data are next available.

The average TST is calculated each day through the summation of total time spent (S) in light sleep, deep sleep, and REM sleep stages as measured by the wearable device for the previous 7 nights divided by the number of nights of sleep (N) captured when N$\geq$4. This rolling 7-day average calculates through the end of the Screening period or when the average TST $\leq$6.5 hours whichever comes first. If N<4, the average TST cannot be calculated (I.e., is not applicable/NA/missing) and will resume when N$\geq$4. For each days' worth of sleep data, the TST for the previous night will be calculated using sleep status reported between 6pm on the previous day through 9am that day.

For a given night, a subject's total sleep may be reported within multiple resting epochs. Each resting epoch is divided into awake, light sleep, deep sleep, and REM sleep categories based on the stage of sleep as measured by the wearable device. For a given day, the nighttime sleep will

be consisted of all sleep epochs ended after 6pm on the previous day and, epochs started prior to 9am on the same day.





Subjects move from Screening to Pretreatment

Once a participant is deemed eligible to be in the Pretreatment period, they should be moved from the Screening period to the Pretreatment period. A participant may become eligible with regards to the sleep assessment portion but not other areas right away or vice versa such that they will only move to the Pretreatment period when all areas of screening have determined eligibility.

Pretreatment/Baseline Sleep Assessment

Visit 1 appointments will be tentatively scheduled during the Screening visit knowing that

screening/washout will vary by subject. At day 1, the 7-day average TST will be calculated using the 7 nights preceding day 1. If the average is ≤7.5 hours they are eligible to enter the Treatment period of the study and this average TST will serve as a subject's baseline sleep assessment in the study, otherwise they are considered a screen failure.

Certificate Of Completion

Envelope Id: 71C96710-AC2A-4013-8953-317B65302465
Status: Completed
Subject: Complete with Docusign: Incyte 902 Statistical Analysis Plan V1.0 22JAN2025.docx
Source Envelope:
Document Pages: 34
Signatures: 5
Envelope Originator:
Certificate Pages: 6
Initials: 0
[redacted]
AutoNav: Enabled
111 Founders Plaza Suite 600
EnvelopeId Stamping: Disabled
East Hartford, CT 06108
Time Zone: (UTC-05:00) Eastern Time (US & Canada)
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[redacted]

Record Tracking

Status: Original
22-Jan-2025 | 15:52
Holder: [redacted]
[redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
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Electronic Record and Signature Disclosure: Accepted: 07-Jan-2025 | 18:20 ID: 7274749f-fe0a-4204-a180-4ae24fa620de		
[redacted] [redacted] [redacted] Biostatistician Premier Research Operations – Regulated Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 4D0BFF36-7935-4880-8B29-0E3D71979512 Using IP Address: 76.232.80.181 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 22-Jan-2025 | 15:58 Viewed: 22-Jan-2025 | 15:59 Signed: 22-Jan-2025 | 16:00
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure