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Statistical Analysis Plan for Interventional Studies

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I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

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1. Glossary of Abbreviations

Abbreviation	Description
AE	adverse event
AESI	adverse event of special interest
ATC	anatomical therapeutic chemical
eCRF	electronic case report form
ET	early termination
HF	human factors
IP	Investigational product
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PPD	postpartum depression
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Standard Data Tabulation Model
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
WHO	World Health Organization

2. Purpose

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

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings.

2.2. Timings of Analyses

The primary analysis is planned after all subjects complete the final study visit or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

3. Study Objectives

3.1. Primary Objective

The primary objective of Study 547-PPD-404 is to evaluate whether the safe-use conditions for administration of ZULRESSO can be implemented in a home setting.

3.2. Secondary Objective

The secondary objective of Study 547-PPD-404 is to identify any process and procedural changes to be implemented for ZULRESSO administration at home.

[redacted]

4. Study Details/Design

4.1. Brief Description

This is an open-label, multicenter study designed to assess the safe-use conditions for administration of ZULRESSO in a home setting to women with postpartum depression (PPD) with the overall goal to improve patient access to ZULRESSO treatment. Up to 50 participants may participate.

This study consists of a screening period of up to 28 days and a 60-hour home infusion of ZULRESSO (Days 1 through 3).

The screening period begins with the informed consent process, which may be conducted electronically. Consented participants will undergo remote or in-person screening procedures to determine eligibility.

During the treatment period, a home healthcare provider will arrive at the eligible participant's home on Day 1 to initiate the 60-hour intravenous (IV) infusion of ZULRESSO. The home healthcare provider must confirm that the participant continues to meet all the eligibility criteria and complete any predose assessments prior to administering the infusion.

The open-label 60-hour infusion will be administered as follows: 30 mcg/kg/hour (Hour 0 to 4), then 60 mcg/kg/hour (Hour 4 to 24), then 90 mcg/kg/hour (Hour 24 to 52), followed by 60 mcg/kg/hour (Hour 52 to 56), and 30 mcg/kg/hour (Hour 56 to 60). A programmable peristaltic infusion pump with alarm is to be used to ensure accurate delivery of ZULRESSO.

4.2. Subject Selection

4.2.1. Inclusion Criteria

Participants must meet all the following criteria to qualify for participation in this study:

1. Ambulatory female ≥18 years of age.
2. Participant has a current diagnosis of PPD, as confirmed by the investigator.
3. Participant agrees not to be the primary caregiver of any dependents during the infusion and must be accompanied by another adult (other than the home healthcare provider) during interactions with their child(ren).
4. Participant has no history of sleep apnea or any clinically significant respiratory conditions.
5. Participant agrees to refrain from the use of central nervous system depressants, such as opioids, benzodiazepines, sleep aids and from drinking alcohol during the infusion.
6. Participant is suitable for administration of ZULRESSO in a home setting, as per the judgement of the investigator.
7. Participant's home is suitable and has necessary provisions for administration of ZULRESSO and meets the following criteria:
    - Safe environment for the home infusion provider staff

- Access to a working telephone
- Electricity and grounded electrical outlets
- Running water
- Access to back-up emergency services (911 service or ambulance availability)
- Sanitary environment

8. Participant agrees to stay at home until the end-of-study visit has been completed, except for a medical emergency.

9. Participant must have a negative pregnancy test at screening and on Day 1 prior to the start of the ZULRESSO infusion.

4.2.2. Exclusion Criteria

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Participant has end stage renal failure.

2. Participant has known allergy to progesterone or allopregnanolone or any excipients in the brexanolone injection.

3. Participant is currently at risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of PPD.

4.3. Determination of Sample Size

The sample size is based on assuming a 7% incidence rate of treatment-emergent adverse events (TEAEs) leading to investigational product (IP) discontinuation or interruption, which is the rate observed in the post-marketing setting. With 50 participants who receive ZULRESSO, the probability is 0.87 for observing at least 2 events; 0.69 for observing at least 3 events, and 0.47 for observing at least 4 events.

4.4. Treatment Assignment and Blinding

This is an open-label study in which all participants will receive ZULRESSO. In this study, participants will be administered a single, continuous, 60-hour, IV infusion of ZULRESSO starting on Day 1.

4.5. Administration of Study Medication

IP will be administered as a single, continuous, IV infusion for 60 hours, by a home healthcare provider in the participant's home. The prepared admixture will be administered at room temperature.

The specific infusion dose of IP will be calculated based on weight (obtained at screening and verified on Day 1 prior to the start of the infusion) for each participant and will be administered according to the dose regimen in Table 1.

Table 1. Infusion Rate

Time point	Day 1 0 to 4 hours	Day 1 4 to 24 hours	Day 2 to 3 24 to 52 hours	Day 3 52 to 56 hours	Day 3 56 to 60 hours
Dose	30 mcg/kg/h	60 mcg/kg/h	90 mcg/kg/h	60 mcg/kg/h	30 mcg/kg/h

The dose regimen will be preprogrammed into the infusion pump by the pharmacist or qualified designee. If necessary, the home healthcare provider may reprogram the pump in consultation with the home infusion provider pharmacy staff for any issues unrelated to safety. If the pump must be reprogrammed during the infusion due to safety, the home healthcare provider must consult the investigator and if necessary, the pharmacist or qualified designee.

The target IV flow rate for the infusion pump is derived from the below formula.

> Pump Flow Rate (mL/h) = [Weight (kg) x Dose Level (mcg/kg/h)] / Solution Concentration (mcg/mL)

The solution concentration is expected to be 1000 mcg/mL of solution.

Dosing should begin in the morning (on Day 1) to allow for recognition of excessive sedation during planned non-sleep periods when the dose increases to 60 mcg/kg/hour and subsequently to 90 mcg/kg/hour.

If excessive sedation occurs at any time during the infusion, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate. The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of hypoxia, the infusion should not be resumed.

For participants who do not tolerate the 90 mcg/kg/hour dose for reasons other than hypoxia, a reduction to 60 mcg/kg/hour may be considered during the time period that the 90 mcg/kg/hour is scheduled to occur.

Any sedation-related AEs that lead to dose interruption, termination, or reduction should be recorded as AESIs. If other intolerable AEs occur, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate.

4.6. Study Procedures and Flowchart

Table 2. Schedule of Assessments

	Screening/ Baseline (Remote or In-person)	**60-Hour ZULRESSO Home Infusion**	**Post-Infusion/ET**
Study Procedure	**Day -28 to Day -1**	**Days 1 to 3 (0 to 60 hours)**	**Day 3 (>60 hours)**
Informed Consent	X		
Inclusion/Exclusion criteria	X	X	

		(confirm participant continues to meet eligibility criteria prior to start of infusion)	
Demographics/medical and surgical history	X		
Body weight/height [1]	X	X (prior to start of infusion)	
Pregnancy test (urine)	X	X (prior to start of infusion)	
Participant training by home healthcare provider		X (prior to start of infusion)	
Vital Signs [2]		X	
ZULRESSO infusion at home		X	
Continuous pulse oximetry (local monitoring) [3]		X	
Remote monitoring of oxygen saturation and heart rate via wireless pulse oximeter		X	
Monitoring for excessive sedation		X (every 2 hours during planned non-sleep periods)	
Daily and/or end-of-shift checklist/journal completed by home healthcare providers to document any use-related issues	X		X
Post-infusion interview of home healthcare provider(s) conducted by HF researchers			X
Home healthcare provider to complete and submit SAE/AESI form(s), if applicable			X (prior to leaving participant's home)
[redacted]			
Adverse Events [4]	X		

Prior/Concomitant Medications [4, 5]	X

Abbreviations: BP = blood pressure; ET = early termination; HF = human factors; HR = heart rate; RR = respiratory rate.

Note: Use of telehealth by the investigator is permitted for the screening visit, in addition to remote assessments conducted during the ZULRESSO infusion, as required.

1 After the participant provides informed consent, a body weight scale will be delivered to the participant's home. The participant will weigh herself on the scale approximately 7 days prior to Day 1 and report her body weight to study personnel. Body weight at screening/baseline is used to calculate ZULRESSO dose and to be confirmed by the home healthcare provider on Day 1 to determine whether any change to ZULRESSO dose is required. Height will be collected at Day 1.

2 Vital signs include BP, RR, HR, and oxygen saturation. Oxygen saturation, RR, and HR collection will begin immediately prior to the start of the infusion and will be monitored continuously through a wearable device. BP will be collected prior to the start of the infusion, and all vital signs will be recorded in the event of excessive sedation, loss of consciousness, or any other adverse event of special interest.

3 Oxygen saturation will only be recorded in the event of excessive sedation, loss of consciousness, hypoxia, or adverse event of special interest (AESI).

4 Information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of medical history, AE collection, and prior/concomitant medication/procedure collection at screening and throughout the study.

5 Prior medications will be collected at screening and concomitant medications and/or procedures will be collected thereafter.

5. Endpoints

5.1. Primary Endpoint

- Incidence of TEAEs leading to dose interruption/discontinuation.

5.2. Secondary Endpoints

- Incidence of nonadherence with the safe-use conditions for administration of ZULRESSO
- Incidence of use-related issues related to the home administration of ZULRESSO
- Incidence of all TEAEs
- Incidence of medication error

It is noted that the endpoints "Incidence of nonadherence with the safe-use conditions for administration of ZULRESSO" and "Incidence of use-related issues related to the home administration of ZULRESSO" will not be analyzed by Syneos Health and are solely listed for completeness. Compliance to safe-use conditions, processes, and procedures will be assessed separately by human factors (HF) researchers.

[redacted]

6. Analysis Sets

6.1. Enrolled Set

The Enrolled Set will include all subjects who provided written informed consent to the study. Screen failures will not be included in this set.

6.2. Safety Set

The Safety Set will include all participants administered ZULRESSO. The Safety Set will be used for all analyses of safety endpoints.

7. General Aspects for Statistical Analysis

7.1. General Methods

- Summaries will be presented for the Safety Set unless otherwise specified..
- Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. The same number of decimal places as the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting standard deviation (SD).
- For categorical endpoints, descriptive summaries will include counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified; the denominator of percentages will be the number of participants in the analysis set used unless specified otherwise.
- No formal significance testing will be performed.
- All relevant participants data will be included in listings. All subjects entered the database will be included in subject data listings.

7.2. Key Definitions

7.2.1. Baseline

Baseline will be defined as the last measurement prior to initiation of the ZULRESSO infusion. Change from Baseline will be defined as the measurement at each time point minus the Baseline value.

7.2.2. Study Day

Study Day is calculated relative to the start date of study treatment and defined as follows:

- The day of participant receiving the first dose of investigational product is designated as Day 1.
- For visit days after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date – Day 1 date. Thus, study days for screening visit are negative numbers. There is no “Day 0”.

The study day will be displayed in all relevant data listings.

7.3. Missing Data

All participants will be used in the analyses using all non-missing data available. No imputation process will be used to estimate missing data.

Dates missing the day, or both the day and month of the year will adhere to the following conventions to classify TEAEs and to classify prior and concomitant medications.

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in derivation. In instances where imputed values will be presented, imputed values will be flagged.

7.3.1. Adverse Events

If an adverse event (AE) start date is completely missing, do not impute the date but consider it as TEAE, unless the AE end date is before the initiation of treatment, in which case the AE will be considered prior.

For partial AE start dates:

- When the year is known, but the month and day is unknown, then:
    - If the year matches the year of first dose date and the end date (if present) is after first dose date, or AE is ongoing, then impute as the month and day of earlier date of (the first dose date + 1 day, last dose date).
    - If the year of AE onset < year of initiation of the treatment, then the month and day will be set to December 31st.
    - If the year of AE onset > the year of initiation of treatment, then the month and day will be set to January 1st.
- If the year and month are known, but the day is unknown, then:
    - If the year of AE onset = the year of initiation of the treatment and:
        - the month of AE onset = the month of initiation of the treatment, then the day will be set to the day of initiation of the treatment.
        - the month of AE onset < the month of initiation of the treatment, then the day will be set to the last day of month of the particular year.
        - if the month of AE onset > the month of initiation of the treatment, then the day will be set to the 1st day of month.
    - If the year of AE onset < the year of initiation of the treatment, then the day will be set to the last day of month of the particular year.
    - If the year of AE onset > the year of initiation of the treatment, then the day will be set to the 1st day of month.
- If the imputed AE onset date is after the AE stop date, then the onset date will be set to the stop date.
    - When the year and day are present and the month is missing, treat it as if the day is missing, and only year is present. Follow the imputation rules for "year is known, but the month and day is unknown".

- When the year is missing, but the month and/or day is known, treat this date as missing; do not impute.

7.3.2. Dates in Disease History (Dates of diagnosis, current episode, first episode)

- If the year is present and the month and day are missing, then the month and day will be set to January 1.
- If the year and day are present and the month is missing, then the month will be set to January.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month

7.3.3. Prior and Concomitant Medications

For the partial start date of medication:

- If the year is present and the month and day are missing, then the month and day will be set to January 1.
- If the year and day are present and the month is missing, then the month will be set to January.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month.
- If the imputed start date of medication is after the end date (imputed date if applicable) of medication, then the start date will be set to the end date of medication.

For the partial end date of medication:

- If the year is present and the month and day are missing, then the month and day will be set to either December 31 or date of death whichever is earlier.
- If the year and month are present and the day is missing, then the day will be set to the last day of the month or month of death.
- If the year and day are present and the month is missing, then treat it as if the day is also missing. Set the month and day to be either December 31 or date of death whichever is earlier.

7.4. Visit Windows

There will be no windowing for visits.

7.5. Pooling of Centers

Not applicable.

7.6. Subgroups

No subgroup analysis is planned for this study.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Subject Disposition and Withdrawals

The summaries of participant disposition will include the number and percentages of participants who were screened, screen failed, treated, completed treatment, discontinued IP prematurely with primary reasons for discontinuing IP, completed the study, and prematurely withdrew from the study with primary reasons for not completing the study. All percentages will be calculated based on the participants who received IP. If a participant is rescreened because the participant has been a screen failure the first time, the status of the participant will be determined from the second screening. In the count of screened participants, such a participant will be counted only once.

A listing will be provided for participants screen failed with primary reason. A separate listing will be provided for the Safety Set and reported for participants who prematurely discontinued IP, prematurely withdrew from the study with reasons, and date of withdrawal from the study.

8.2. Protocol Deviations

All major protocol deviations will be summarized using the Safety Set. All protocol deviations (major and minor) will be included in a data listing for the Enrolled Set.

Any violation of inclusion/exclusion criteria will also be presented in a separate data listing using the Enrolled Set.

8.3. Demographic and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics (e.g., weight, height), will be summarized and listed using the Safety Set. The below conversions will be used if needed.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

Body Mass Index (kg/m^2) = Weight(kg)/[Height$(m)^2$]

8.4. Medical/Surgical History

Medical and surgical history collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The summary will be presented by primary system organ class (SOC) and preferred term (PT). A Participant will be counted once within each level of summarization. Medical and surgical history will be listed. A separate listing will be provided for information regarding diagnosis, isolation, and/or hospitalization due to COVID-19.The MedDRA preferred terms used to code and identify COVID-19 are listed in Appendix C.

8.5. Disease History and Psychiatric History

The following analyses will use the Safety Set.

Disease history such as the diagnosis of PPD, current or past episode, date of delivery, onset date of PPD and hospitalization will be listed.

Participant history of psychiatric disorders will be tabulated for each pre-defined psychiatric condition and if existed within the past 12 months. A corresponding listing will be provided.

8.6. Prior and Concomitant Medications

Medications will be recorded throughout the duration of the study and may be coded using World Health Organization (WHO) Drug dictionary Global B3 March 2020, or later.

Medications taken prior to the initiation of the start of IP will be denoted “Prior”. Those medications taken prior to the initiation of the IP and continuing beyond the initiation of the IP, or those medications started at the same time or after the initiation of the IP will be denoted “Concomitant”.

Both prior and concomitant medications will be separately summarized by anatomical therapeutic chemical (ATC Level 3) class and preferred name. All prior and concomitant medications will be listed. Medications will be presented according to whether they are “Prior” or “Concomitant”, as defined above. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant. Missing date imputation rules are provided in Section 7.3.3.

Concomitant procedures are recorded on a separate electronic case report form (eCRF) page; this will be presented in a listing by participant.

The Safety set will be used for all tables and listings.

8.7. Extent of Exposure

The number and percentage of treated subjects receiving 60 hours of infusion will be tabulated. Detailed information regarding the infusion timepoints, planned doses, actual infusion rates, infusion interruptions, infusion discontinuations, and dose changes will be listed for each participant.

8.8. Treatment Compliance

Not applicable.

9. Safety

Safety data will be listed by participant and summarized. All safety summaries will be performed on the Safety Set.

9.1. Adverse Events

Adverse events will be coded using MedDRA Version 24.0 or higher. A TEAE is defined as an AE with onset on or after the start of IP. If the date of an adverse event is incomplete and an unambiguous determination could not be made with respect to its onset time versus the first dose of IP and/or last dose of IP, the adverse event will be assumed to be a TEAE. For imputation of missing AE dates, please refer to Section 7.3.1.

If a medication error results in an AE, the resulting AE will be recorded and reported. The medication error itself will also be coded using the appropriate MedDRA Version 24.0 or higher.

An overview summary table of TEAEs will present the number and percentage of participants as well as the number of events for the following:

- TEAEs
- TEAEs by maximum severity (severe>moderate>mild)
- Study drug related TEAEs
- Treatment-emergent Serious Adverse Event (SAE)
- TEAEs leading to interruption/discontinuation of IP
- TEAEs leading to withdrawal from the study
- TEAEs leading to dose reduction
- TEAEs leading to death

Incidence of TEAEs in following categories will be provided by SOC and PT. A participant is counted only once under each SOC and PT in case of multiple occurrences of the same AE. These tables will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

- TEAE
- TEAEs by maximum Severity
- TEAEs by relationship
- Serious TEAEs
- TEAEs leading to interruption/discontinuation of IP

- TEAEs leading to withdrawal from the study
- TEAEs leading to dose reduction or interruption

For maximum severity, participants will be counted only once within each SOC and PT at the maximum severity in the following order: severe> moderate> mild; an AE with missing severity will be omitted from severity presentation. For relationship to IP, participant will be counted only once within each SOC and PT at the strongest relationship to IP in the following order: related > not related, an AE with relationship missing is treated as related.

All AEs through the end of the study will be listed including, but not limited to, verbatim term, PT, SOC, relationship to study drug, start and end date, seriousness, action taken, and outcome. Separate listings will be provided for SAEs, AEs associated with death, AEs associated with study treatment discontinuation, and AEs leading to dose reduction. TEAEs will be flagged in the listing.

9.1.1. AESIs

An AESI is an AE/SAE of scientific and/or medical concern, specific to the product or program for which ongoing monitoring and rapid communication by the investigator to the sponsor is required. The following events are considered AESIs and collected as an AESI.

- Excessive sedation
- Loss of consciousness
- Any sedation-related AE that leads to dose reduction, interruption, or termination

All AESIs (including those with onset or worsening before the start of IP) will be separately summarized and listed, in addition to being included in the primary TEAE tables discussed above. Also, [redacted] Excessive sedation and loss of consciousness will be reported in a listing for the information including the timepoint, whether the participant was assessed for excessive sedation, and the date and time.

9.2. Vital Signs and Oxygen Saturation

Vital signs data collected by the remote monitoring system includes blood pressure, respiratory rate, heart rate, and oxygen saturation. This system will capture data every two seconds and these data will transferred to Sage Therapeutics in both unaggregated and aggregated formats. The unaggregated format will include all available measurements on all participants receiving ZULRESSO. The aggregated format will include the mean, median, 10th, and 90th percentiles calculated on 15-minute blocks of time that are aligned with the 0-15 minute, 15-30 minute, 30-45 minute, and 45-60 minute quadrants of a standard clock face. For convenience, these data (both unaggregated and aggregated) may be referred to as “automated” vital signs data.

Vital signs data may also be collected directly by the home healthcare provider(s) and recorded in the EDC system, particularly if a study participant experiences an Adverse Event of Special Interest (AESI) or hypoxia. For convenience, these data may be referred to as “manual” vital signs data.

Vital signs data will be listed and summarized only for AESIs and/or hypoxia. For convenience, these may be referred to as "events of interest". The MedDRA preferred terms used to code and identify hypoxia are listed in Appendix B. The event of interest time frame will begin two (2) minutes prior to the event onset to two (2) minutes after the event of interest has stopped. Events of interest not having a stop time will not be considered for these listings and summaries.

- EXAMPLE: If a participant experiences the onset of an event of interest at 8:20 am and the event of interest stops at 8:59 am, the event of interest time frame begins at 8:18 am and extends to 9:01 am.

  The first 15-minute block of time used for aggregating purposes will be the 8:15 – 8:30 am clock dial quadrant and the last 15-minute block of time used for aggregating purposes will be the 9:00 – 9:15 am clock dial quadrant.

  There will be four (4) median values for each measured vital sign corresponding to four (4) 15-minute blocks of time and these blocks of time will be labeled '0-15 mins', '15-30 mins', '30-45 mins', and '45-60 mins' for tabulation purposes.

  If the home healthcare provider(s) take manual vital signs measurements at 8:25 am and 8:40 am, differences between the aggregated median values and manual measurements will be calculated for the '0-15 mins' and '15-30 mins' blocks of time.

For each event of interest, the following will be done:

- Unaggregated automated vital signs data will be listed by minute for the event of interest time frame (defined above) along with the manual vital signs data. In the unlikely event that the date and time of manual vital signs data collection includes a non-trivial measurement of seconds, the time will be rounded to the nearest minute.

- The aggregated median of automated vital signs data for each 15-minute window having any overlap with an event of interest time frame (defined above) will be compared to the manual vital signs data. This will be done by calculating the difference(s) between the median within a 15-minute window and whatever manual vital signs data exist within the same 15-minute window. These differences will be summarized by event of interest, vital sign, and 15-minute timepoint. See detailed example above..

9.3. Nonadherence with Safe-Use Administration of ZULRESSO

The incidence of nonadherence with the safe-use conditions for administration of ZULRESSO will not be analyzed in this SAP. Analysis of these data will be performed by Human Factors.

9.4. Use-related Critical Issues Related to the Home Administration of ZULRESSO

The home healthcare provider will report any use-related issues of ZULRESSO. This will not be analyzed in this SAP.

9.5. Medication Error

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of any healthcare professional, patient, or consumer.

For the purposes of this study, a medication error can therefore occur anytime on or after a pharmacist prepares the IV bags for shipment to the participant's home.

The medication error analyses described in the SAP are limited to data available from the adverse event form in the EDC system. Additional information may be available from Human Factors reports and/or safety narratives.

Medication errors are captured on the adverse event EDC form and coded using the same version of MedDRA that applies to adverse events. The specific MedDRA preferred terms used to code and identify medication errors are listed in Appendix A and medication errors will *not* be included in TEAE tables, but rather handled separately.

The incidence of medication error will be summarized using the same format as the TEAE overview summary table and will present the overall number and percentage of participants experiencing medication error, as well as the number and percentage of participants experiencing each specific preferred term. The number of events will also be included.

All medication errors must be recorded and sent to Sage or designee within 24 hours of the site becoming aware of the medication error. The medication error must be reported to Sage or designee even if the medication error does not result in an AE. The lower level term "medication error" should be avoided unless there is no other information reported about the medication error. Instead, a more specific term should be provided.

If a medication error results in an adverse event, the adverse event should be handled separately and also entered on the EDC adverse event form.

9.7. Urine Pregnancy Test

A urine pregnancy test will be conducted for all participants at screening and again on Day 1 prior to the start of the infusion. Unscheduled pregnancy tests will be conducted as needed. Results of the pregnancy test will be listed.

10. Interim Analyses

Not applicable.

11. Changes from Analysis Planned in Protocol

None.

12. Reference List

Clinical study protocol, version 2.0, Amendment 1, 23 June 2021, Company: Sage Therapeutics Inc.

13. Programming Considerations

All TFLs, and statistical analyses will be generated using SAS for Windows, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Computer-generated table, figure and listing (TFL) output will adhere to the following specifications.

13.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output
- 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 or portable document format pdf
- Numbering of TFLs will follow ICH E3 guidance

13.2. Table, Figure, and Listing Format

13.2.1. General

- All TFLs will be produced in landscape format.
- All TFLs will be produced using the Courier New font, size.
- 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.
- 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).
- 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.
- 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., cm2, Cmax) 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.

13.2.2. Headers

- All output will have the following header at the top left of each page:
- Sage Therapeutics, Inc. Protocol 547-PPD-404 (Syneos Health study number 7027123)

- Draft/Final Run

- 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

13.2.3. 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 Analysis Set)

13.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy 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, include 'unit' in 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 subjects in the analysis set

- The order of treatments in the tables and listings will be Placebo first in the case of placebo-controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable)

13.2.5. Body of the Data Display

13.2.5.1. *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.

13.2.5.2. *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 each 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 and so 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 subjects
- 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
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-value will be presented to 4 decimal places with p-values less than 0.0001 reported as “<0.0001”. P-values larger than 0.9999 will be reported 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%)). < Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places.> Unless otherwise noted, for all percentages, the number of subjects 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 preferred term), drugs (by ATC1 code), and adverse events (by preferred term) 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 which cannot be estimated will be reported as '-'

- The percentage of subjects will normally be calculated as a proportion of the number of subjects 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, usually the appropriate number of subjects exposed. Details will be described in footnotes or programming notes, as necessary

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will be added describing whether the subject 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 system organ class) must be split over more than one page, output the subheading 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

13.2.5.3. *Listing Conventions*

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

- Missing data will be represented on subject 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 subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject 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

13.2.5.4. *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

13.2.6. 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
- Subject 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

14. 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 produced output.

15. Shells

Tables, listings, and figure shells are provided in a separate file.

Appendix A

MedDRA v24.1 Preferred Terms to Identify Medication Errors
Accidental device ingestion
Accidental device ingestion by a child
Accidental exposure to product
Accidental exposure to product by child
Accidental exposure to product by elderly person
Accidental exposure to product packaging
Accidental exposure to product packaging by child
Accidental overdose
Accidental poisoning
Accidental underdose
Accidental use of placebo
Booster dose missed
Circumstance or information capable of leading to device use error
Circumstance or information capable of leading to medication error
Complication of device insertion
Complication of device removal
Complication of drug delivery system removal
Contraindicated device used
Contraindicated product administered
Contraindicated product prescribed
Contraindication to medical treatment
Contraindication to vaccination
Deprescribing error
Device adhesion issue

Device connection issue
Device deployment issue
Device difficult to use
Device dispensing error
Device infusion issue
Device maintenance issue
Device malfunction
Device monitoring procedure not performed
Device placement issue
Device programming error
Device use confusion
Device use error
Device use issue
Device-device incompatibility
Discontinued product administered
Documented hypersensitivity to administered product
Dose calculation error
Drug administered in wrong device
Drug delivery system issue
Drug delivery system malfunction
Drug dispensed to wrong patient
Drug dose omission by device
Drug dose titration not performed
Drug effective for unapproved indication
Drug ineffective for unapproved indication

Drug monitoring procedure incorrectly performed
Drug monitoring procedure not performed
Drug titration error
Duplicate therapy error
Expired device used
Expired product administered
Exposure to contaminated device
Exposure via contaminated device
Exposure via direct contact
Exposure via eye contact
Exposure via ingestion
Exposure via inhalation
Exposure via partner
Exposure via skin contact
Exposure via unknown route
Extra dose administered
Failure of child resistant product closure
Failure to suspend medication
Implantation complication
Inadequate aseptic technique in use of product
Inappropriate schedule of product administration
Inappropriate schedule of produce discontinuation
Incomplete course of vaccination
Incorrect disposal of product

Incorrect dosage administered
Incorrect dose administered
Incorrect dose administered by device
Incorrect dose administered by product
Incorrect drug administration rate
Incorrect product administration duration
Incorrect product dosage form administered
Incorrect product formulation administered
Incorrect route of product administration
Injury associated with device
Intercepted accidental exposure to product by child
Intercepted medication error
Intercepted product administration error
Intercepted product dispensing error
Intercepted product monitoring error
Intercepted product preparation error
Intercepted product prescribing error
Intercepted product selection error
Intercepted product storage error
Intercepted wrong patient selected
Interchange of vaccine products
Labelled drug-disease interaction issue
Labelled drug-disease interaction medication error
Labelled drug-drug interaction issue

Labelled drug-drug interaction medication error
Labelled drug-food interaction issue
Labelled drug-food interaction medication error
Lack of administration site rotation
Lack of application site rotation
Lack of infusion site rotation
Lack of injection site rotation
Lack of vaccination site rotation
Medical device monitoring error
Medication error
Multiple use of single-use product
Needle issue
Occupational exposure to product
Occupation exposure to radiation
Overdose
Paravenous drug administration
Poor quality device used
Poor quality product administered
Prescribed overdose
Prescribed underdose
Product adhesion issue
Product administered at inappropriate site
Product administered by wrong person
Product administered to patient of inappropriate age

Product administration error
Product administration interrupted
Product appearance confusion
Product barcode issue
Product commingling
Product communication issue
Product compounding quality issue
Product confusion
Product delivery mechanism issue
Product design confusion
Product dispensing error
Product dispensing issue
Product dosage form confusion
Product dosage form issue
Product dose omission in error
Product dose omission issue
Product expiration date issue
Product identification number issue
Product label confusion
Product label issue
Product label on wrong product
Product lot number issue
Product monitoring error
Product name confusion

Product packaging confusion
Product packaging difficult to open
Product packaging issue
Product preparation error
Product preparation issue
Product prescribing error
Product prescribing issue
Product reconstitution quality issue
Product selection error
Product storage error
Product substitution error
Product temperature excursion issue
Product use complaint
Product use in unapproved indication
Product use in unapproved therapeutic environment
Product use issue
Prosthetic cardiac valve malfunction
Radiation overdose
Radiation underdose
Recalled product administered
Single component of a two-component product administered
Syringe issue
Therapeutic drug monitoring analysis incorrectly performed
Therapeutic drug monitoring analysis not performed

Therapeutic product effective for unapproved indication
Therapeutic product ineffective for unapproved indication
Transcription medication error
Transfusion with incompatible blood
Treatment noncompliance
Underdose
Unintentional medical device removal
Unintentional use for unapproved indication
Vaccination error
Wrong device used
Wrong dosage form
Wrong dosage formulation
Wrong dose
Wrong drug
Wrong patient
Wrong patient received product
Wrong product administered
Wrong product procured
Wrong product stored
Wrong rate
Wrong route
Wrong schedule
Wrong strength
Wrong technique in device usage process

Wrong technique in product usage process

Appendix B

MedDRA v24.1 Preferred Terms to Identify Hypoxia
Hypoxia
Oxygen saturation decreased
Oxygen saturation abnormal

Appendix C

MedDRA v24.1 Preferred Terms to Identify COVID-19
Anti-platelet factor 4 antibody positive
Antiviral prophylaxis
Antiviral treatment
Asymptomatic COVID-19
Breakthrough COVID-19
Congenital COVID-19
Coronavirus infection
Coronavirus pneumonia
Coronavirus test
Coronavirus test negative
Coronavirus test positive
COVID-19
COVID-19 immunisation
COVID-19 pneumonia
COVID-19 prophylaxis
COVID-19 screening
COVID-19 treatment
Exposure to communicable disease
Exposure to SARS-CoV-2
Multisystem inflammatory syndrome
Multisystem inflammatory syndrome in adults
Multisystem inflammatory syndrome in children

Occupational exposure to SARS-CoV-2
Pneumonia viral
Post-acute COVID-19 syndrome
SARS-CoV-2 antibody test
SARS-CoV-2 antibody test negative
SARS-CoV-2 antibody test positive
SARS-CoV-2 carrier
SARS-CoV-2 RNA
SARS-CoV-2 RNA decreased
SARS-CoV-2 RNA fluctuation
SARS-CoV-2 RNA increased
SARS-CoV-2 RNA undetectable
SARS-CoV-2 sepsis
SARS-CoV-2 test
SARS-CoV-2 test false negative
SARS-CoV-2 test false positive
SARS-CoV-2 test negative
SARS-CoV-2 test positive
SARS-CoV-2 viraemia
Suspected COVID-19
Thrombosis with thrombocytopenia syndrome
Vaccine derived SARS-CoV-2 infection

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