STATISTICAL ANALYSIS PLAN

Ghrelin (OXE--103) for Acute Concussion Management
NCT04558346

Version History:	**Version 1.0, November 30, 2020**

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List of Abbreviations

4MBS	4 most bothersome symptoms (on the PCSS)
AE	Adverse event
CCM	Center for Concussion Management
CTCAE	Common Terminology Criteria for Adverse Events
DAE	AE leading to study drug discontinuation
ECG	Electrocardiogram
FDA	Food and Drug Administration (United States)
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IND	Investigational new drug
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PCSS	Post-Concussion Symptom Score questionnaire
PGAS	Patient Global Assessment of Status
PHQ-9	Patient Health Questionnaire
PP	Per protocol
PT	Preferred term
QOLIBRI	Quality of Life after Brain Injury questionnaire
ROC	Receiver operating characteristic
SAE	Serious AE
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SOC	System-organ class
TE	Treatment-emergent
UU	Unanticipated or unexpected
VAS	Visual analog scale

1. Introduction

This statistical analysis plan (SAP) provides details on the study design, outcome measures and data analyses planned for the exploratory study of ghrelin (OXE-103) in subacute and acute concussion management that is being conducted at the University of Kansas Health System Center for Concussion Management (CCM). The outcome measures and data analyses specified in this SAP supersede any specified in the study protocol, if differences exist.

Any deviations from this plan will be documented in the clinical study report, and will include timing of changes in relation to unblinding of the study.

Pharmacokinetic, anti-ghrelin antibody and/or biomarker samples may be collected for future use and any data analysis will be the subject of a separate SAP.

2. Study Design

This subacute and acute concussion management study will be conducted as a randomized, single center, double-blind, placebo-controlled, parallel group design in two distinct parts. In Part A, subjects will be recruited from the University of Kansas Health System CCM clinics which include Neurology, Sports Medicine, and Neurosurgery/Physical Medicine and Rehabilitation. Subjects who provide written informed consent and satisfy enrollment criteria at the end of a 7-day screening period will be randomized in a 1:1 manner to either the OXE-103 or placebo treatment groups. In Part B, subjects will be recruited from the emergency department and enrolled within 24 hours of injury. Treatments will be self-administered subcutaneously twice daily during a 14-day treatment period; the OXE-103 group will receive 40 µg/kg with each dose.

For Part A, clinic visits will be conducted at the start of Screening (Day -7), Randomization (Day 1), Day 8, End of Treatment (Day 15), 1 week after the end of treatment (Day 21) and End of Study (Day 44). Phone contacts will be done during Screening (Day -3) and during treatment (Days 4 and 11). Part B subjects will follow the same schedule except that there will be no screening visit or phone contact. Outcomes for the investigation of the effect of OXE-103 will be based on self-reported symptom scoring, quality of life questionnaires, computerized cognitive testing assessing executive function, memory and processing speed, and accelerometer-based balance scoring. Safety assessments will include collection of adverse events, clinical laboratory samples, electrocardiograms (ECGs), vital signs including body weights, suicide screening and physical/neurological examination findings.

3. Study Objectives

The primary objective of this study is to describe the change in symptom burden of subacute or acute concussion for the two treatment groups in each part, as measured by the change from baseline to Day 15 in the Post-Concussion Symptom Score questionnaire (PCSS) total score, total number of symptoms and total score for the 4 most bothersome symptoms (4MBS, as identified on Day 1). Improvements of ≥20% will be considered clinically meaningful.

The secondary objectives are to:

- Describe the change in quality of life for the two groups in each part as measured by the change from baseline to Day 15 in the Quality of Life after Brain Injury (QOLIBRI) total score and Patient Global Assessment of Status Visual Analog Scale (PGAS VAS).
- Describe changes in cognitive performance for the two groups in each part as measured by the change from baseline to Day 15 in the BrainCheck composite score.

Exploratory objectives of the study are to:

- Describe the correlation between the change in symptom burden and quality of life during the treatment period for each group in each part.
- Describe changes in symptom burden and quality of life at different time points for the two groups in each part.

4. Sample Size

The exploratory nature of this study is such that it is not powered to yield statistically significant outcomes, but will allow detection of trends within subjects and between groups within each part, will support comparison with standard tests of neurocognitive functions, and will provide sample size estimates for future studies of individuals with acute or persistent concussion related symptoms.

The study will enroll a maximum of 50 subjects in each part, but may stop recruiting if each group has at least 20 participants who have completed the study.

5. Outcome Measures

5.1 Primary Efficacy Outcome Measures

- PCSS severity responder as defined by ≥20% improvement over baseline at Day 15 in the severity score
- PCSS symptom responder as defined by ≥20% improvement over baseline at Day 15 in the number of symptoms
- PCSS 4MBS responder as defined by ≥20% improvement over baseline at Day 15 in the 4MBS severity score
- Change from baseline in PCSS severity score at each post-baseline assessment (Days 4, 8, 11, 15, 21 and 44)
- Change from baseline in PCSS number of symptoms at each post-baseline assessment (Days 4, 8, 11, 15, 21 and 44)
- Change from baseline in PCSS 4MBS severity score at each post-baseline assessment (Days 4, 8, 11, 15, 21 and 44)

5.2 Secondary Efficacy Outcome Measures

- Change from baseline in QOLIBRI total score at each post-baseline assessment (Days 4, 8, 11, 15, 21 and 44)
- Change from baseline in PGAS VAS at each post-baseline assessment (Days 4, 8, 11, 15, 21 and 44)
- Change from baseline in BrainCheck composite score at each post-baseline assessment (Days 4, 8, 11, 15, 21 and 44)

5.3 Exploratory Efficacy Outcome Measures

The exploratory study objectives may be assessed by examining responder rates on days other than the assessments done at the end of treatment (Day 15) or by examining relationships between primary and secondary outcomes. Therefore, there are no additional efficacy outcome measures to define.

5.4 Safety Outcome Measures

Any laboratory, vital sign or ECG result meeting Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, will be included in adverse event (AE) reports. Any unexpected findings on physical or neurological examinations will also be included in AE reports.

- Occurrence of any AEs commonly reported for OXE-103, CTCAE Grade 1 (mild) only.
- Occurrence of any unanticipated or unexpected (UU) treatment-emergent (TE) AE, UU serious AE (TE-SAE), UU AE leading to study drug discontinuation (TE-DAE), UU TE-AE related to study drug and UU TE-AE classified as Grade 2 or higher according to CTCAE, version 5.0. [Note that any AE commonly reported for OXE-103 that has CTCAE Grade 2 (moderate) or higher will be included among the UU TE-AEs.]
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- Change from baseline in clinical laboratory parameters at each post-baseline assessment (Days 8, 15 and 21)
- Change from baseline in vital signs (including body weight) at each post-baseline assessment (Days 8, 15 and 44)
- Change from baseline in ECG intervals at each post-baseline assessment (Days 8, 15, 21)
- Change from baseline in Patient Health Questionnaire (PHQ)-9 total score at each post-baseline assessment (Days 8, 15 and 44)

6. Statistical Methods

6.1 General Methods

This pilot study will describe changes observed in the two treatment groups, placebo versus OXE-103, separately for each part. Since the study is exploratory, analyses will focus on descriptive comparative statistics and not on a pre-specified statistically significant primary endpoint. Data will be used to enable power calculations and the definition of suitable clinical endpoints for further clinical development. Data from baseline and on Study Days 4, 8, 11, 15, 21, and 44 will be analyzed. Note that day definitions in this study will follow the Clinical Data Interchange Standards Consortium in that there is no Day 0;

assessments performed prior to randomization will be done on Days -7 and -3 (Part A only) and randomization is considered Day 1.

For all evaluations of changes from baseline, baseline is defined as the last reported value before the first dose of study drug. In most instances, this will be the value recorded on Day 1.

For the evaluation of safety, a treatment-emergent finding is any result that is newly reported after the first dose of study drug. This may include an existing condition which worsens in severity after the start of treatment.

Continuous variables such as total score or change from baseline will be summarized by the number of observations, mean, standard deviation, median, minimum and maximum value. Graphs of changes from baseline over time will present the means and 95% confidence intervals.

Binary or categorical variables will be summarized by the number of observations in each category along with the percent of observations.

To aid in interpretation of the importance of relationships, correlation coefficients (Pearson and Spearman) will be reported with p-values.

6.2 Analysis Sets

The intent-to-treat (ITT) analysis set is defined as all randomized subjects. This analysis set will be used for demographics and baseline characteristics, entrance criteria violations and other protocol deviations, study drug exposure and prior/concomitant medications summaries.

Since this is an exploratory study being conducted for the purpose of signal detection, the per protocol (PP) analysis set will be used for all efficacy summaries. This set is defined as all patients who completed at least 10 doses) of treatment, had a Day 8 PCSS assessment and no major protocol deviations.

The safety analysis set is defined as all subjects who received at least one dose of study drug. This analysis set will be used for all safety summaries, and subjects will be included in the treatment group which represents the treatment actually administered. If there are no errors in dosing (ie, each subject received the treatment to which he/she was randomized), it is anticipated that the safety analysis set will be the same as the ITT analysis set because it is expected that all randomized subjects will be dosed.

6.3 Subject Accountability

The number of subjects screened will be summarized along with the reasons for screen failure. The number (%) of subjects randomized, treated, completing treatment, completing study and in each analysis set will be summarized by treatment group. Reasons for not completing treatment and/or study will also be summarized by treatment group.

6.4 Entrance Criteria Violations and Other Protocol Deviations

The number (%) of subjects randomized in violation of each entrance criterion (if any) will be summarized by treatment group. In addition, the number (%) of subjects for whom a pre-specified protocol deviation was observed will be summarized by treatment group.

6.5 Demographic and Baseline Characteristics

Age at randomization, sex, race, ethnicity and days since injury will be summarized with appropriate statistics for each treatment group. Days since injury will be calculated as randomization date – injury date. Age and days since injury will also be summarized categorically (Age: 18-25, 26-35, 36-45 and 46-55 years; Days since injury: ≤7, 8-14, 15-21, 22-28, >28 days).

Medical history/concurrent conditions will be summarized for each treatment group by International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnoses obtained from BioPortal [1,2]. In this summary, a subject may be counted only once for each distinct diagnosis.

6.6 Study Drug Exposure

The total number of doses self-administered by each subject will be summarized as both a continuous and categorical (≤7, 8-14, 15-21, 22-28 doses) variable and presented for each treatment group.

6.7 Prior and Concomitant Medications

A prior medication is defined as any medication reported in use by the patient prior to randomization. A concomitant medication is defined as any medication either in use at randomization which was allowed to be continued during the treatment period, or, one that is started post-randomization and prior to the end of study. One medication report may be identified as both a prior and a concomitant medication.

Prior and concomitant medications will be summarized for each treatment group by generic name as determined by RxNORM ontology in BioPortal. In these summaries, a subject may be counted only once for each unique medication.

6.8 Efficacy Analysis

As described previously, binary variables (responders) and continuous variables (values and changes from baseline) will be summarized with appropriate descriptive statistics for each treatment group and each visit (as needed). Changes from baseline over time will also be presented graphically with means (95% confidence intervals) with both treatment groups presented on the same figure.

To evaluate the appropriateness of the current responder definitions, a Receiver Operating Characteristic (ROC) analysis will be performed for each response outcome measure. The current definitions indicate that a ≥20% improvement over baseline is required for a subject to be considered a responder. In the ROC analysis, the percent improvement will be varied from 5% to 95% to determine which percentage is best for distinguishing OXE-103 treated subjects from placebo subjects. If data suggest an early treatment response, the ROC analysis may be performed for a time point earlier than Day 15.

FDA pre-IND guidance from the FDA on the clinical development of OXE-103 advised that "***The outcome measure should be constructed in a way that ensures that a score change is indicative of a meaningful improvement in how a patient feels or functions that comes from a treatment effect specific to mild TBI.***" Pearson and Spearman correlation coefficients (and p-values) will be calculated to examine

relationships between the PCSS changes and changes in the quality of life measures (QOLIBRI total score and PGAS VAS).

Relationships between PCSS changes and changes in cognition and balance (BrainCheck composite measure) will also be examined using correlation coefficients.

6.9 Safety Analysis

AEs commonly reported for OXE-103 will be summarized for each treatment group, by study day of assessment and will include an 'At any time' category.

An overview of UU AEs will provide the number (%) of subjects in each treatment group with any TE-AE, TE-SAE, TE-DAE, TE-AE related to study drug,, and TE-AE classified as Grade 2 or higher according to CTCAE, version 5.0. Additionally, TE-AEs, related TE-AEs and Grade 2 or higher TE-AEs will be summarized for each treatment group by Medical Dictionary for Regulatory Activities (MedDRA) system-organ class (SOC) and preferred term (PT) as obtained from CTCAE, version 5.0. In these summaries, a subject may be counted only once for each PT and SOC. Details for any TE-SAEs or TE-DAEs will be provided in individual subject data listings.

Clinical laboratory test, vital sign (including body weight), ECG and PHQ-9 values and changes from baseline will be summarized with appropriate descriptive statistics for each treatment group and each visit.

6.10 Missing Data Handling

For responder analyses, the last available post-baseline value will be used for patients who do not have an assessment on Day 15. No other data will be imputed.

6.11 Visit Windows

Assessments during the treatment period (Days 4 to 15) that are not obtained on the scheduled day will be assigned to the nearest scheduled day. For example, a PCSS assessment performed on Day 12 will be assigned to Day 11 for the purposes of 'by visit' summaries, unless the assessment was inadvertently obtained in addition to the Day 11 assessment.

Assessments after the end of treatment that are not obtained within the scheduled window will be assigned to the nearest scheduled day (Day 21 or 44). For example, if the QOLIBRI assessment was not obtained until Day 25, it would still be assigned to Day 21 for the purposes of 'by visit' summaries.

6.12 Subgroup Analyses

No subgroup analyses are currently planned for this exploratory study.

6.13 Adjustment for Covariates

No statistical modeling is planned for this exploratory study, therefore, there will be no adjustment for covariates.

6.14 Interim Analyses

There are no plans for any unblinded interim analyses. Unblinding will occur after the last subject has completed or discontinued from each part of the study, and the study database for that part has been cleaned and locked.

It is anticipated that blinded data review will occur during to study in order to ensure that assumptions which served as the basis for planned analyses are appropriate.

6.15 Statistical Software

Data analysis will be conducted using Statistical Analysis System (SAS), Version 9.4.6.16 References

[1] The National Center for Biomedical Ontology was founded as one of the National Centers for Biomedical Computing, supported by the NHGRI, the NHLBI, and the NIH Common Fund under grant U54-HG004028. Musen MA, Noy NF, Shah NH, Whetzel PL, Chute CG, Story MA, Smith B; NCBO team. The National Center for Biomedical Ontology. J Am Med Inform Assoc. 2012 Mar-Apr;19(2):190-5. Epub 2011 Nov 10.

[2] Whetzel PL, Noy NF, Shah NH, Alexander PR, Nyulas C, Tudorache T, Musen MA. BioPortal: enhanced functionality via new Web services from the National Center for Biomedical Ontology to access and use ontologies in software applications. Nucleic Acids Res. 2011 Jul;39(Web Server issue):W541-5. Epub 2011 Jun 14.