Ghrelin (OXE--103) for Acute Concussion Management

NCT04558346

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Summary of Changes and Rationale

The List of Changes table below lists modifications to the current protocol (as per amendment 1.6).

List of Changes – Amendment 1.7

Page(s)	Modification(s)
1-2	**Intro** – Summary of the Changes and Rationale of modifications
12 12 10-11	**Proposed Clinical Trial** • For Part B change start of treatment criteria from 24 hours from time of injury to within 24 hours of presentation to Trauma Unit. • Modify Part A to an open-label treatment arm (OXE-103) compared to a non-treatment concurrent control arm. Maintain Part B randomized and blinded, OXE-103 versus placebo. • Added flowsheets depicting Day 1 study activities for both Parts A & B (including the two arms of Part A: open-label treatment and non-treatment concurrent control).
13 13	**Specific Aim 1** • The Part A open-label treatment arm will enroll up to 30 participants but will stop recruiting when Part A has 20 participants who complete the study. • The Part A non-treatment concurrent control arm will enroll a minimum of 20 participants who complete the study but may continue to recruit beyond 20 while the open-label arm is still recruiting. **Specific Aims 1-4** • Corrects use of terms Day 14 to Day 15 and Day 45 to Day 44. This reflects the visits as listed on the Schedule of Events.
14 15 16	**Inclusion/Exclusion** • Increase the upper limit for age to 60-years-old from 55-years-old. • The seven-day screening period for Part A has been removed. Part A participation, including study drug treatment, now begins on Day 1. The removed screening period occurred from Days -7 to 1. For clarity there is no screening period for the Part B acute study; participation already begins on Day 1. • Removes gamma-glutamyl transferase lab exclusion criteria, because this lab is not available as part of the UKHS standard chemistry panel. • Allows for procedures/labs performed prior to study participation as part of subject's normal care to be used for study.
15	**Study Procedures** • Restatement of change for Part A from randomization to OXE-103 or placebo to open-label treatment with OXE-103 and a non-treatment

15-16 17 17 16 16 17	concurrent control arm. • Revision of recruitment goals for Part A. Previously it was 40 for Part A and 40 for Part B, with a maximum of 50 subjects in each Part. Now, Part A is revised to have a target of 30 for the treatment Arm (Arm 1) and 20 for the non-treatment Arm (Arm 2), with opportunities for additional Arm 2 enrollment. The maximum for Part A Arm 1and Part B combined is 80 subjects. • Modified the visit schedule language to allow for the Part A Arm 2 non-treatment subjects' schedule. • Study visits for the Part A non-treatment concurrent control group not requiring correlative lab draws or study equipment return may be conducted via telemedicine at the discretion of the Principal Investigator. • Removal of the seven-day screening period and adjusted language to reflect that activities for both Parts start on Day 1. • Removal of required abstinence from other mTBI treatments and therapies during study participation. • Removal of safety monitoring language for Part A non-treatment Arm.
18	**Cardiovascular and Respiratory Risk -** ECG recording will not be collected for the Part A non-treatment concurrent control arm.
19	**Laboratory & Endocrine Risks** • Laboratory testing for safety will not be required for participants in the Part A non-treatment concurrent control arm, however, correlative lab collection for this arm will occur on Days 1 and 15. • Removal of gamma-glutamyl transferase lab language (lab not available as part of the UKHS standard chemistry panel.
18	**Contraception and Women of Childbearing Potential** – Adds language to allow for serum pregnancy testing. Due to laboratory testing limitations, this change was required.
23-25 24	**Schedule of Events** • Study table has been modified to eliminate the Part A screening period, add relevant evaluations to Day 1, and to separate out Part A Arms to clarify that safety monitoring activities will not be done on Part A non-treatment Arm 2 (includes adverse event recording, lab testing, and ECG's). • Adds reference that both serum and urine pregnancy tests are allowed. • Adds clarification to footnote language regarding assessments and questionnaires done on Days 1 and 8 are to be done prior to dispensing drug. This allows for dosing of drug by subjects prior to study visit on Day 8. • Clarifies that clinically significant abnormal labs will be repeated until normalized to allow for lab values that may present as abnormal but not clinically significant. • Adds reference to remote or in-person clinic visits for the Part A Arm 2 non-treatment group for visits Days 8 and 21.

	• Clarifies that correlative labs collected includes biomarkers.
19 19 20	**Outcomes & Study Tools** • Removal of screening period language for Part A. • Added for clarity that language applies to both acute and sub-acute concussions. • Corrects visit dates for BrainCheck testing to match what was previously listed in the Schedule of Events.
21	**Statistical Analysis—**Removes reference to baseline visit for emphasis that there is not a screening period.

Ghrelin (OXE--103) for acute concussion management

HSC #: 145983

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***Summary*:**

Ghrelin is a naturally occurring hormonal peptide with extensive preclinical and clinical safety data to supporting the safety of OXE-103 for studies in patients with concussion/m TBI. In addition, Ghrelin has been shown in many preclinical and clinical studies to potentially target many different areas of concussive injury including energy regulation, inflammation, and axonal connectivity. There have been no clinical studies looking at ghrelin as treatment for acute concussion. If there are indeed benefits, the societal impact could be huge.

Overview

Management of concussions and mild traumatic brain injury is a high priority medical focus, social concern, and research topic. Currently, there are no FDA approved treatments for acute concussion. Current standard of care starts with cognitive rest followed by a gradual return to normal activity as symptoms abate. We will investigate use of the hormone ghrelin (OXE-103) as treatment for symptoms of acute concussion. Our initial goal is to show improvement in the way patients feel or function via assessment of post-concussion related symptoms. We expect the findings from this pilot to support larger Phase II studies of efficacy for symptom management, and potential treatment of underlying neurologic injury.

Oxeia Biopharma Inc. will donate the drug supply for this study. The clinical safety, product characterization and manufacturing information presented herein has been extracted from an open FDA IND on OXE-103. The open IND will be cross referenced for regulatory submissions prepared for this study.

A. Background & Rationale

Introduction:
Concussions are the leading form of mild traumatic brain injury. The CDC reported the U.S. population sustains 1.7 million concussions annually and although underreported by as much as 80% the annual rate of concussion has more than doubled in the past decade [1]. There are currently no evidence-based treatments for concussion. The current standard of care is cognitive rest followed by gradual return to normal activity. Treatment is based on symptom management, which has varying efficacy, while waiting for the underlying injury to repair itself.

Pharmacology and Mechanism of Action:
At the neuronal level, a concussion causes a well-established neurometabolic cascade. Brain injury results in a massive efflux of potassium out of the neuron and an influx of calcium into the neuron. At the same time, there is a depolarization event that results in release of glutamate. This glutamate then causes toxicity to surrounding neurons. Meanwhile the injured neuron tries to achieve homeostasis by pumping calcium out of the cell and co-transporting potassium into the cell. These events result in expenditure of energy--glucose in the form of ATP. This results

in an energy crisis. Mitochondrial respiration is disrupted and formation of ATP is impaired. This leads to oxidative stress (Reactive Oxygen Species--ROS) and inflammation. The direct injury also causes disrupted axonal transport, swelling, and reduces neuronal connectivity [2].

OXE-103 is a 28 amino-acid polypeptide hormone produced semi-synthetically and is identical to endogenous ghrelin secreted by the stomach. It is also secreted by the hypothalamus and possibly other brain regions [3]. Ghrelin binds to the growth hormone secretagogue receptor (GHSR-1a) and is the only known peripherally-produced orexigenic hormone. The amino acid sequences of ghrelins are well conserved across species, indicative of its biological importance. The physiological and pharmacological effects of ghrelin are thought to be diverse, pleiotropic and complex, including growth hormone secretion, appetite stimulation, regulation of energy balance, acceleration of gastric emptying, stimulation of gastrointestinal motility, neuroprotection, and regulation of the immune system, as well as regulation of the cardiovascular system [4]. Of direct relevance to this study, ghrelin directly impacts the neurometabolic cascade by increasing glucose availability, increasing mitochondrial ATP, and decreasing ROS by uncoupling protein 2 (UCP-2) pathway. It increases axonal potentiation and synaptic number thereby increasing axonal connectivity [5]. Recent nonclinical studies of ghrelin as a neuroprotective intervention in several central nervous system models report increased mitochondrial respiration and synaptic density; and reduced ROS, inflammation, and tau protein phosphorylation.

Ghrelin activates the AMPK pathway. AMPK turns on ATP producing pathways and increases mitochondrial biogenesis. The binding of ghrelin to the GHSR-1 receptor increases mitochondrial membrane protein UCP-2 expression. UCP-2 directly “uncouples” oxidative phosphorylation thereby decreasing ROS generation, and increases mitochondrial generation and respiration [5]. Ghrelin increases mitochondrial respiration and decreases ROS [4].

UCP2 and GHSR-1 knockout model studies have separately reported UCP2 overexpression as neuroprotective [6], and enhanced mitochondrial respiration and reduction in reactive oxygen species after ghrelin administration to be UCP-2 dependent [5]. Furthermore, ghrelin directly increases the synaptic density of the hippocampus [5], which is particularly sensitive to volume loss after concussion/mTBI in an athletic population [7]. Improved memory and neurocognition are also observed with ghrelin treatment [8]. Taken together, ghrelin’s effects are specifically relevant to limiting post concussive metabolic impairment and its consequential neurotoxicity.

An observational human study has also identified a positive correlation between acute serum ghrelin levels and measures of improved neurocognitive function after concussion. In the study, 118 patients presenting to a large research hospital were included based on concussion diagnosis and followed for 90 days. All patients underwent blood collection at Day 0, 1 and 2 following enrollment and serum samples were retained for subsequent analysis. Neurocognitive testing including memory, reaction time, visual tracking and attention was conducted. Day 90 neurocognitive scores were used to distinguish patients into better and worse performing cohorts. Out of eight endogenous hormones analyzed, only ghrelin was shown to be an independent predictor of three-month cognitive outcome. Patients with higher endogenous ghrelin levels were less likely to have cognitive impairment compared to those patients with lower endogenous ghrelin levels based on ROC analysis (AUC = 0.904, $p < 0.001$) [5].

These clinical and nonclinical reports of ghrelin’s effects support its potential as a novel neuroprotective treatment when administered following acute concussion/mTBI.
The neuroprotective effects of ghrelin were recently observed in TBI mice models using a controlled weight drop apparatus. Acute intraperitoneal (IP) ghrelin administration (10 µg ghrelin

per dose), twice on the day of injury result in significantly higher UCP-2 levels, less loss of brain volume 7 days following injury ($p<0.05$), significantly less apoptosis in the neurocortex and hippocampus, decreased invasion of inflammatory cells, and, significantly, with respect to potential beneficial effects in clinical trials, improved motor function up to 7 days after injury ($p<0.001$) [9, 10]. Furthermore, the neuroprotective action of ghrelin in TBI is dependent on binding to the GHSR-1 receptor [11].

In a mouse model of TBI using a controlled cortical impactor with standardized settings for milder injury [12], subcutaneous ghrelin administration (10 µg ghrelin per dose) at 10 minutes and one hour after injury significantly reduced ROS. Animals (n = 5 per group, 3 groups) were sacrificed 24 hours after injury and whole brain ROS was assessed by a flow cytometer oxidative burst assay. Treatment with ghrelin significantly decreased oxidative burst as compared to sham and vehicle treated groups ($p<0.05$). HOCL formation (myeloperoxidase staining) and neutrophil infiltration (Gr-1 staining) in the hippocampus were also notably reduced versus sham and vehicle treated groups [13].

OXE-103 neuroprotective activity has been demonstrated in commonly used animal model for ALS (transgenic mice that overexpress the mutant human superoxide dismutase 1 [SOD1] gene ($SOD1^{G93A}$ mice) [14, 15]. In this model, the number of motor neurons was assessed after 7 weeks of OXE-103 treatment (50 µg/day, SC infusion) from 10 weeks of age. The number of motor neurons in sections of the spinal cord was significantly higher in the OXE-103 treated group when compared with the vehicle treated group, indicating that OXE-103 protected against degeneration of motor neurons in the spinal cord of $SOD1^{G93A}$ mice.

GLP Safety and Toxicology: Extensive preclinical GLP toxicology and safety studies have been conducted by Daiichi Sankyo. Single dose repeat dose (13, 26, and 39 weeks), genotoxicity, reproductive toxicology and developmental toxicology studies have been conducted across rats, monkeys, and rabbits (see Appendix 1).

Clinical Safety:
The safety, tolerability and pharmacokinetics of OXE-103 has been evaluated in 9 clinical studies, with IV and SC routes of administration. This includes 6 studies with OXE-103 administered as either an IV bolus or IV infusion and 4 studies using SC injection. The safety of OXE-103 administered SC has been evaluated with doses up to 80 µg/kg/day in 205 subjects and the safety of IV administered OXE-103 has been evaluated with doses up to 8 µg/kg/day in 139 subjects. OXE-103 has been reported to be well tolerated in higher doses and for longer durations, relative to the dose and duration of OXE-103 in the proposed clinical trial. The observations made in clinical trials conducted thus far support the proposed dose of 40 µg/kg bid for 14 days in this clinical study. All clinical trial information is included in the open IND at the FDA (see Appendix 1).

Drug Interactions:
No significant drug interactions with agents used in neurologic intensive care units have been identified for OXE-103.

P1 Data, Pharmacodynamics, Pharmacokinetics, Dose Selection:
A Phase 1 safety and PK study in 50 healthy male and female volunteers has been conducted via both intravenous and subcutaneous routes of administration at several doses. Pharmacodynamic markers included Growth Hormone (GH), ACTH, cortisol, prolactin, glucose, and insulin. Ghrelin was shown to have a benign safety profile for both routes of administration.

Exposure increased in a dose-related manner for IV and SC dosing. The most direct PD marker, GH, was dose related and demonstrated maximal levels between 20-45ug/kg which indicated saturation of ghrelin receptors. These data inform dosing levels that are metabolically active and are supported by preclinical dosing levels from neurometabolic as well as neurogenic models.

Safety Concern	**Safety Data**
ECG	Investigator's Brochure **4.1.2.2 Effects on the Cardiovascular and Respiratory Systems:** Continuous IV infusion of OXE103 (up to 1000 µg/kg/hr) in conscious, unrestrained monkeys resulted in a transient increase and then decrease in blood pressure in 1 of the 4 monkeys evaluated. None of the animals had changes in heart rate, ECG parameters, respiratory rate, arterial blood pH, blood gas tensions, hemoglobin oxygen saturation, body temperature or clinical signs. **Table 5.9 Summary of Safety Results from Phase 2 studies with SC Treatment of OXE103:** **12-lead ECGs:** no clinically meaningful changes in ECG in Study ASBI303 (n=6), ASBI304 (n=17), and ASBI307 (n=151)
Complete blood count, metabolic panel, coagulation panel	Investigator's Brochure **Table 8.8 Summary Tables For Clinical Studies:** **Japan Phase 1 NA 1401 (n=42)**: No SAEs reported. The TEAEs, regardless of causality, occurring in >1 subject from any individual treatment group or from combining the OXE103 treatment groups were clinical TEAEs of feeling hot, hot flush, and sweaty; chemistry and urine laboratory TEAEs included bilirubin total increased, creatinine decreased, HDL C decreased, LDH decreased, indirect bilirubin increased, urate increased, protein total decreased, urine WBC increased, and urine ketone body present; complete blood count TEAEs included lymphocyte percentage decreased, neutrophil percentage increased, WBC count decreased, and WBC count increased. Single IV administration of OXE103 up to 8.0 µg/kg was generally well tolerated.

Safety Concern	Safety Data
	5.4.2.9: Clinical Laboratory Evaluations: In ASBI 303(n=6), there were no laboratory abnormalities reported as TEAEs. In ASBI 304 (n = 17), the hematology, serum chemistry, urinalysis, and coagulation results were unremarkable. **Table 5.9 Summary of Safety Results from Phase 2 studies with SC Treatment of OXE103** **Assessment of laboratory tests (hematology, chemistry, urinalysis, and coagulation)**: There were no clinically meaningful changes from baseline at any visit in the active treatment groups compared to placebo for any of the hematology, chemistry, urinalysis. Study ASBI303 (n=6), ASBI304 (n=17), and ASBI307 (n=151)
Pregnancy in females of childbearing potential	OXE-103 is a polypeptide composed of 28 amino acid residues produced semi-synthetically and is structurally identical to the human endogenous ghrelin. According to data derived from reproductive toxicity studies summarized in the OXE-103 Investigator's Brochure: *Section 1.4 Nonclinical Toxicology (paragraph 5)* *No effects were observed on fertility in rats, on reproductive function in parental rats and maternal rabbits, or on embryo-fetal development in rats or rabbits by IV administration. In addition, no effects were observed on maternal rabbits and on embryo-fetal development in rabbits by SC administration. In an IV-dose study on pre- and postnatal development including maternal function in rats, a tendency to increase in body weights of live newborns was noted at 300 µg/kg/day or more as pharmacological effects of OXE103.* The complete toxicology reports can be found under Oxeia's existing IND (120694).
Other labs related to ghrelin (including possibly growth hormone, insulin, ICF-1, ACTH, cortisol and prolactin)	Investigator's Brochure: **5.3 Clinical Pharmacology:** Serial blood samples were obtained for pharmacokinetic and pharmacodynamic evaluations of ghrelin, desacyl-ghrelin, growth hormone (GH) and insulin growth factor-1 (IGF-1) in 6 of the 9 studies

Safety Concern	Safety Data
	(ASBI 301 (n=6), ASBI 303 (n=6), ASBI 304 (n=17), NA 1401(n=42), NA 1501(n=12) and NA 1502 (n=6). **Additional data from studies referenced in 5.3 above:** In addition to the data referenced above, serum samples for GH and IGF-1 was also assessed in ASBI 307 n=142. Additional PD markers not mentioned above were also assayed across the 9 studies include: prolactin n=72, ACTH n=72, cortisol n=214, catecholamines n=89, insulin n=89, glucose n=225, A1C n=159, FSH n=12, LH n=12, CRP n=165, NT-proBNP n=6, IL-6 n=159, IL-1B n=17, TNF n=159. GH consistently increased proportional to the dose of OXE103; IGF-1, prolactin, and ACTH either showed increases which returned to baseline within 3 hours of dosing or showed no difference to placebo; the remaining PD markers showed no changes attributed to administration of OXE103. The conclusions across the 9 studies were that no safety issues related to these biomarkers and the administration of OXE103 was observed. **5.4.2.1 Overall safety Evaluation:** glucose tolerance testing was done in studies ASBI 304 (n=17) and ASBI 307 (n= 151) since it has been reported that ghrelin can suppress insulin release and cause insulin resistance [Garin et al. 2013]. No obvious relationship was observed between 2-hour postload value from OGTT (mmol/L; Day 8) and predicted AUCss (pg·h/mL; Day 85) of OXE103. **Appendix 1: Tabular Summaries of OXE103 NonClinical Studies:** GH Secretion, Non-GLP, Study PBC 79-44 (n=4M): OXE103 did not significantly increase plasma prolactin and ACTH concentrations

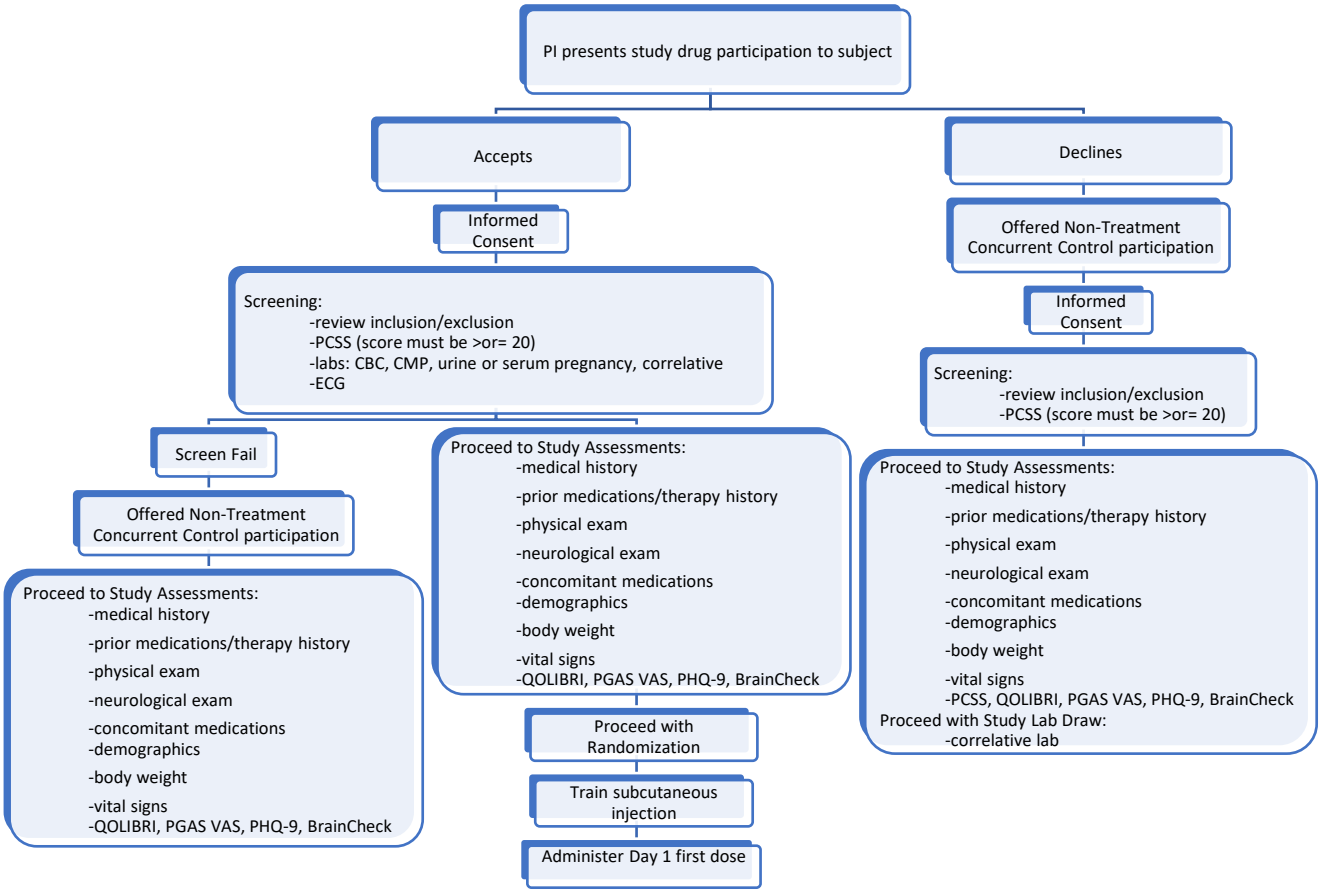
Safety Concern	Safety Data
Published Studies	There is extensive published literature on over 100 clinical studies administering ghrelin via intravenous infusion or bolus. The patient populations in these studies include: Healthy, obese, gastrectomy, cancer, hypopituitarism, metabolic syndrome/diabetes, anorexia nervosa/ bulimia nervosa, pulmonary disease, gastroparesis, hyperthyroid, renal disease, heart failure, cushing's syndrome, PCOS, functional dyspepsia, acromegaly, hyperparathyroid, osteoarthritis, and major depression disorder. Garin et.al 2013 (reference supplied upon request). These studies support the benign safety profile of OXE103 and are consistent with data generated in the Phase 1 and Phase 2 clinical studies.

PART A: POST-ACUTE DAY 1

Subjects are presented with study drug (OXE-103) treatment. If they decline, they will be offered participation in non-treatment control Arm. If subjects choose treatment and fail screening, they may be offered non-treatment control Arm option.

PART A ARM 1 = OXE-103 treatment

PART A ARM 2 = Non-treatment concurrent control

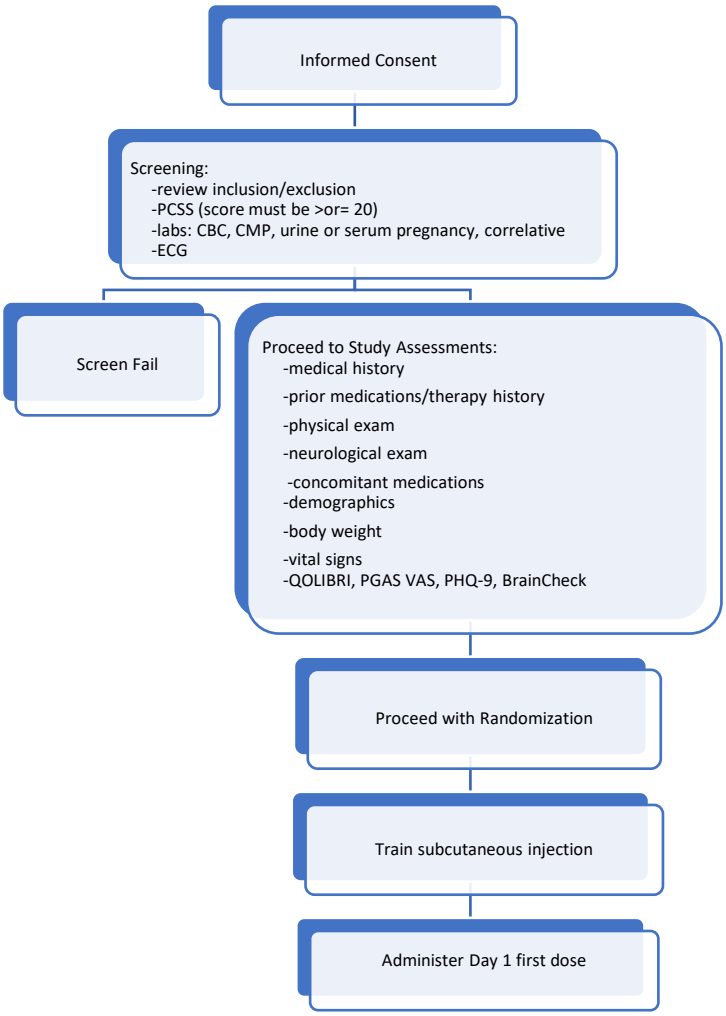


PART B: ACUTE DAY 1

Subjects choosing to participate in study are randomized to receive study drug (OXE-103) or placebo.

PART B ARM 1 = OXE-103

PART B ARM 2 = Placebo



Regulatory:
Oxeia's license through Daiichi Sankyo includes cross-reference to an open IND at the FDA. In November 2017 Oxeia submitted a pre-IND briefing package for a proposed Phase 2 study. The FDA response supported moving into Phase 2. This study will be conducted under an investigator sponsored IND cross referencing the existing open FDA IND.

Manufacturing, Partnerships, Current GMP Drug Supply:
The company maintains access to clinical grade drug supply manufactured by Daiichi Sankyo, Ltd. for subcutaneous injection. Multiple lots have been produced and are available for clinical study use. The drug product is manufactured in compliance with good manufacturing practice. It is supplied in a 5 mL clear, borosilicate glass vial with a butyl-rubber closure (fluoro-resin film laminated), as a sterile lyophilized white powder or cake equivalent to 14 mg of OXE-103 as the active ingredient and sucrose (inactive ingredient). Matching placebo and diluent product is also available.

OXE-103 drug product, placebo, and diluent should be stored refrigerated between 2°C to 8°C (35.6°F to 46.4°F). Reconstituted OXE-103 for SC administration 14 mg (in 5 mL multi-use vials) is stable for up to 14 days at 10°C or for up to 3 days when stored at 25°C/1000 Lux. The reconstituted drug product (and placebo) should be stored refrigerated at 2°C to 8°C (35.6°F to 46.4°F).

Upon request from the study team, Oxeia Biopharmaceuticals will coordinate shipment of all necessary study drug product, placebo, and diluent to the study team. Shipments will include all appropriate certificates of quality, as may be necessary for any FDA-related audits and submissions.

Proposed Clinical Trial
We propose a pilot study to treat 1) Sub-acute concussion with OXE-103 in Part A and 2) Acute concussion management with OXE-103 within 24 hours of presentation to the Trauma Unit in Part B. For Part A, we will recruit subjects from the University of Kansas Health System Center for Concussion Management (CCM) clinics which include Neurology, Sports Medicine, and Neurosurgery/PM&R. For Part B, we will recruit subjects from the University of Kansas Health System Trauma Unit. In Part A we will compare an open-label treatment arm (OXE-103) to a non-treatment concurrent control arm. Part B will be randomized double blind 1:1 to treatment with OXE-103 and placebo. We will compare these using self-report symptom scoring, quality of life questionnaires, computerized cognitive testing assessing executive function, memory and processing speed, and accelerometer-based balance scoring. The exploratory nature of this study is not powered to yield statistically significant outcomes, but will allow detection of trends within subjects and between groups, will support comparison with standard tests of neurocognitive functions, and will provide sample size estimates for future studies of people with persistent concussion related symptoms.

This study is highly relevant clinically and uniquely suited to being conducted at the CCM. It will be the first to test ghrelin as therapy for sub-acute concussion.

Specific Aims:

1. **Describe the change in symptom burden in sub-acute (Part A) and acute (Part B) concussion for the two groups.** This aim defines our primary objective. In Part A we will enroll a maximum of 30 subjects in the open-label treatment Arm (OXE-103) but will stop recruiting when that arm has 20 participants who have completed study requirements. All Part A participants must be diagnosed with a concussion and experience persistent concussion symptoms $\leq$ 28 days post injury. The Part A non-treatment concurrent control Arm will enroll a minimum 20 participants who complete the study requirements, but may continue to recruit more than 20 participants while the Part A open-label treatment Arm is still recruiting. In Part B we will enroll a maximum of 50 subjects but will stop recruiting after each arm (OXE-103 Arm and placebo Arm) has 20 participants who have completed the study requirements. In Part A subjects will receive OXE-103 open-label and in Part B we will randomize 1:1 to placebo versus OXE-103. The Post-Concussion Symptom Score questionnaire (PCSS) will be used as an overall measure of symptom burden. The number of symptoms and severity at each time point are also measures of interest. In addition, subjects will be asked to identify and rank the 4 most bothersome symptoms. We hypothesize that changes in these most bothersome symptoms may have a higher correlation to improvement in quality of life. A visual comparison of change in the two groups will be made. We will consider a change of 20% to be clinically meaningful. Our primary aim will describe the change in symptoms between day 1 and day 15.

2. **Describe the change in quality of life between the two groups.** This aim defines one of our secondary objectives. To assess this, we will administer the Quality of Life after Brain Injury scale (QOLIBRI) and a Patient Global Assessment of Status (PGAS). A change of 20% will be considered clinically meaningful. Our primary objective with this aim will assess the change between days 1 and 15.

3. **Describe the correlation between the change in symptom burden and quality of life.** This is an exploratory aim. We hypothesize that improvement in symptom burden will correlate with improvement in quality of life measures. This may be more evident in the correlation between the change in the 4 most bother symptoms and quality of life measures. This aim will describe this correlation between days 1 and 15.

4. **Describe changes between symptom burden and quality of life at different time points.** This is an exploratory aim. We will collect data at days 21 and 44 to allow for comparisons at later time points. This may be used to describe changes in these measurements at time points after administration of OXE-103. It is hypothesized that the effects of OXE-103 are long standing and therefore worsening after administration should not occur. We will have data to compare day 15 to days 21 and 44.

5. **Describe changes in cognitive performance between the two groups.** This aim defines one of our secondary objectives. Improvement in cognitive functioning could correlate with underlying improvement in neuronal function. We will assess cognitive function with BrainCheck, a digital assessment tool, at specified intervals. This tool is administered via iPad and can be administered in clinic with supervision by trial personnel as well as at home by the subject.

Benefits/Risks of research

Benefits: Currently rest is the initial treatment for concussion. Therapies that can be prescribed later (there is no consensus as to when to start these—tends to range from a couple of weeks post-injury to a couple of months) include physical/vestibular therapy (but this takes time and may provoke symptoms initially), and symptomatic treatment of symptoms with medications. The effectiveness of these drugs to provide potential treatment of underlying neurometabolic changes versus purely symptomatic relief is unknown. Further, each medication comes with potential for adverse events. Providing a safe treatment that is effective at reducing symptoms, increasing quality of life, and potentially providing treatment for underlying neurometabolic dysfunction would be innovative and change the current paradigm of concussion care.

Risks: Previous studies have shown that OXE-103 is quite safe. This study will help to confirm that safety profile in this clinical population. Long term use of ghrelin can lead to increased appetite, weight gain, and adiposity [16]. However, we will mitigate that risk by using OXE-103 for a short period and we will obtain weight measurements at regular intervals during drug treatment.

Inclusion/Exclusion:

Subjects will be both men and women, ages 18-60 years old, with a concussion resulting from a direct or indirect blow, rotation, or whiplash injury to the head or body. For the purposes of this study, we will define diagnosis of concussion/mTBI as those who have met the criteria set forth in this classification schema [23]:

Severity of Traumatic Brain Injury			
	GCS	PTA	LOC
Mild	13-15	<1 day	0-30 mins
Moderate	9-12	>1 to < 7 days	>30 mins to < 24 hrs
Severe	< 9	> 7 days	> 24 hrs

*GCS=Glasgow Coma Scale; PTA=Post-Traumatic Amnesia; LOC=Loss of Consciousness

However, as noted by the American Congress of Rehabilitation Medicine's statement on the definition of mTBI, "Due to the lack of medical emergency, or the realities of certain medical systems, some patients may not have the above factors medically documented in the acute stage. In such cases, it is appropriate to consider symptomatology that, when linked to a traumatic head injury, can suggest the existence of a mild traumatic brain injury [24]. When available, the study team will use medical records to confirm a patient's injury as an mTBI according to the schema above, however, if no records exist or are obtainable, clinical history and symptomatology will be used to confirm the diagnosis.

In Part A, subjects must be consented ≤ 28 days post injury. In Part B, subjects must be consented, randomized, and start treatment within 24 hours of presentation to the Trauma Unit.

Subjects in both Part A and B will have a symptom severity score of ≥ 20 at the time of randomization in order to reduce the expected degree (number and severity) of spontaneous symptom resolution prior to study completion.

Subjects with pre-existing neurologic conditions other than mTBI (including cognitive dysfunction) will be excluded.

Subjects with concurrent long bone fractures or orbital fractures will be excluded.

Subjects receiving, or planning to receive, a continuous ketamine infusion while enrolled in study will be excluded.

Subjects with these known endocrinological abnormalities at baseline will be excluded from study: diabetes mellitus, excess or deficiency of growth hormone, cortisol, or prolactin. Exclusion from study for any other endocrinological abnormalities or diagnoses existing at baseline are ultimately up to the discretion of the study physician.

Significant abnormalities in serum creatinine (>2.5 mg/dL), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal, or bilirubin (>2.5 mg/dL) will exclude subjects from participation.

Subjects with any abnormal findings noted on imaging, such as hemorrhage, will be excluded from the study. Subjects who meet criteria for moderate or severe TBI will also be excluded.

Subjects who are known to be pregnant will be excluded. Subjects who do not agree to double-barrier contraception or abstinence (for female subjects of child-bearing potential or male subjects who are sexually active with a female of child-bearing potential) until the day following last dose (total of at least 5 half-lives) will be excluded.

In Part A subjects receiving other concomitant medications, physical therapy, or other treatments related to their current mTBI will be eligible if they meet the inclusion criteria. Subjects (or household members) who are not able to inject themselves or the subject will be excluded. Ultimately study subject participation will be at the discretion of the study physician.

For both Part A and Part B, subjects are not allowed to be concurrently enrolled in another therapeutic intervention clinical trial while participating in this study. Any subjects currently enrolled in such a separate therapeutic intervention clinical trial, for any condition, will be excluded from participating in this study. For clarification, this does not include observational clinical trials or registries.

Procedures and labs performed as part of the subject's normal medical care (not for study) within one day prior to consent may be allowed to be used for study. This includes items such as CBC, CMP, ECG, and pregnancy testing.

Study Procedures:
General study design:

We propose an open-label design for the sub-acute Part A. Arm 1 will receive OXE-103 and Arm 2 will be a non-treatment concurrent control. Both Arms of Part A will each have a target of 20 subjects who will complete the study requirements. In Arm 1 (open-label treatment) an additional 10 subjects may be enrolled to replace any subjects that do not complete the study requirements. In the event that Arm 2 (non-treatment control) has reached its minimum target of 20 completed subjects and Arm 1 (open-label treatment) is still recruiting, then Arm 2 may continue to enroll subjects until Arm 1 reaches its target enrollment.

In Part B the design will be randomized, double-blinded, and placebo-controlled with Arm 1 receiving OXE-103 and Arm 2 receiving placebo. The enrollment target will be 20 subjects receiving OXE-103 and 20 subjects receiving placebo. Up to 50 subjects may by enrolled in Arms 1 and 2 combined to allow for replacement of subjects who may not complete the study requirements.

In Part A Arm 1 and Part B both Arms 1 & 2, the maximum enrollment will be 80 subjects. For the Part A Arm 2 (non-treatment concurrent control) the minimum target enrollment will be 20 subjects, but there will be no maximum number.

We will randomize using the REDCap database. The database will be set up to share randomization allocation only with the statistician and Investigational Pharmacy. All subjects will be consented and either begin treatment within 24 hours of presentation to the Trauma Unit (for Part B) or ≤28 days post-injury (for Part A). For Part A, starting on Day 1, the treatment cohort (Arm 1) will receive OXE-103 40ug/kg twice daily by self-injection and the non-treatment control group (Arm 2) will begin their monitoring. For Part B, on Day 1 (within 24 hours of being admitted into the Trauma Unit) the treatment Arm will receive OXE-103 40ug/kg SC twice daily by self-injection and the placebo Arm will receive a placebo injection SC twice daily. OXE-103 and placebo will be maintained and dispensed by Investigational Pharmacy. Subjects will receive an 8-day supply of syringes pre-loaded with OXE-103 or placebo. Each cohort receiving OXE-103 or placebo will receive the 2nd set of syringes with OXE-103 or placebo at the Day 8 visit. Appropriate therapy that would be considered standard of care by the Principal Investigator or Co-Investigator will be administered or prescribed at any time during subjects' study participation.

Subject training

Subjects will be provided with instructions for SC self-administration of OXE-103 and placebo. Subjects will be trained to inject themselves and need to demonstrate competency by self-administering the first dose of the study drug at the study site. Alternatively, if a subject is accompanied by a reliable and willing household member, that individual will be trained to administer study drug to the subject and will be required to demonstrate competency at the study site. If neither self-administration nor administration by a household member is feasible the subject will be deemed ineligible to participate. Subjects will also be instructed on storage of the drug/placebo according to the parameters. A study team member will document the storage location for each subject enrolled. Subjects will be asked to inject the first daily dose in the morning, after eating. The second dose will occur in the evening, again after eating. The study team may provide injection diaries to subjects in order to document dosing.

Recruitment:

Subject recruitment for Part A will take place among patients seen in Dr. Rippee's Center for Concussion Management (CCM) clinic located at The University of Kansas Health System (TUKHS), Landon Center on Aging, Department of Neurology. Subject recruitment for Part B will take place among patients seen by the TUKHS Trauma team. Patients meeting the study's

inclusion/exclusion criteria will be invited to participate in the study. If they are interested, a study team member will meet with the patient to discuss the study in more detail. Informed consent will be sought; when obtained, subjects will be screened for study risks and other exclusion criteria. Subjects enrolled in Part B of the study by the Trauma team will be followed after discharge from the hospital in Dr Rippee's clinic; the remainder of their study visits will be completed with Dr. Rippee in his ambulatory clinic. Part A Arm 1 (non-treatment control) study visits may be conducted via telemedicine at the discretion of the Principal Investigator, Dr Rippee, with the exception of Study Days 1 and 15 when correlative labs will need to be drawn, and Day 44 when study iPads will need to be returned to the study team.

In the event that subjects are enrolled by the Trauma team into Part B while having an inpatient status at TUKHS, the study team, Investigational Pharmacy, and the medical team will work together to dispense, store, and administer the study medication. The study team will continue to work with the Investigational Pharmacy and medical team, as appropriate, for the duration of the subject's inpatient status while on study, as necessary to comply with this protocol.

Attrition: This is a pilot study and no previous data exists as a basis to estimate attrition for this study. Any study participant who withdraws consent or is removed from Part A or Part B of the study during the 28-day trial period or does not successfully complete the protocol required 14 days of dosing may be replaced to allow for 40 subjects who complete the protocol.

Target Duration: The target duration of the treatment intervention with OXE-103 will be two weeks. The total involvement in the study including screening and follow up assessments will be 8 weeks.

Adverse Events: Oxeia, the supplier to the study team of the OXE-103 and placebo, performs and submits safety reports to the FDA under a separate IND. As OXE-103 has already undergone safety testing and the safety profile is known, the adverse events associated with OXE-103 are included in an Investigator's Brochure written by Oxeia Biopharmaceuticals. For the purposes of this study, the study team will collect all adverse events reported by subjects including SAEs and TEAEs regardless of suspected causality, and in accordance with appropriate rules and regulations. Study team will report any that are deemed by Investigator to be:

- Unexpected AND related
- Expected but occurring at an increased frequency or severity
- Occurring in such a way that changes the risks/benefit ratio to study participants and warrants an update in consent form and/or protocol.
- All SAE's will be reported per applicable rules and regulations (IRB/FDA)

Depression Screening: The study team will administer the PHQ-9 questionnaire at specified timepoints to help identify any potential risk or need for intervention.

Safety Monitoring: Subjects participating in Part A Arm 2 (non-treatment control) will not require safety monitoring. All other subjects participating in Part A Arm 1 and Part B Arms 1 & 2 will require safety monitoring.
Vital signs including temperature, heart rate, and blood pressure will be obtained at all clinical visits. Body weight, physical exam, and neurological exam will also occur at all clinical visits.

Dr. Richard Dubinsky, MD, MPH will serve as an independent medical monitor. The study team will submit all adverse events reported to Dr. Dubinsky for review after 10 subjects are enrolled and again after 30 subjects are enrolled.

Contraception and Women of Childbearing Potential:
OXE-103 is a polypeptide composed of 28 amino acid residues produced semi-synthetically and is structurally identical to the human endogenous ghrelin. According to data derived from reproductive toxicity studies summarized in the OXE-103 Investigator's Brochure:
Section 1.4 Nonclinical Toxicology (paragraph 5)
No effects were observed on fertility in rats, on reproductive function in parental rats and maternal rabbits, or on embryo-fetal development in rats or rabbits by IV administration. In addition, no effects were observed on maternal rabbits and on embryo-fetal development in rabbits by SC administration. In an IV-dose study on pre- and postnatal development including maternal function in rats, a tendency to increase in body weights of live newborns was noted at 300 µg/kg/day or more as pharmacological effects of OXE103.

The complete toxicology reports can be found under Oxeia's existing IND (120694).

Given that ghrelin naturally exists within and is produced by the body, along with the reproductive toxicology study data, the study team will not exclude patients who may have childbearing potential. However, all female participants will undergo a urine or serum pregnancy test at screening. Any subjects who are pregnant will be excluded. Further, all female subjects of child-bearing potential and male subjects sexually active with a female of child-bearing potential will be required to use double-barrier contraception or practice abstinence during the 14 day treatment period with ghrelin and for 24 hours after the final dose. The half life of ghrelin is 30 minutes, therefore this will be more than 5 half lives after the final dose.

Cardiovascular and Respiratory Risks:
Pre-clinical studies performed with OXE-103 showed that, continuous IV infusion of OXE-103 (up to 1000 µg/kg/hr) in conscious, unrestrained monkeys resulted in a transient increase and then decrease in blood pressure in 1 of the 4 monkeys evaluated. None of the animals had changes in heart rate, ECG parameters, respiratory rate, arterial blood pH, blood gas tensions, hemoglobin oxygen saturation, body temperature or clinical signs.

Additionally, results from the Phase 2 study as noted in Oxeia's Investigator's Brochure showed no clinically meaningful changes with regard to ECG and subcutaneous treatment with OXE-103. Results are summarized on Table 5.9 of the Investigator's Brochure, which can be cross referenced under Oxeia's existing IND (120694).

All participants will have vital signs, including heart rate and blood pressure, monitored at each clinical visit. Further, an ECG will be acquired at visits 1 through 4. This will be acquired using AliveCor's Kardiastation digital 6 lead ECG. Kardiastation is a Class II medical device cleared by the FDA for acquiring ECGs in the physician office. Kardiastation uses a HIPPA compliant smartphone app and cloud based database for storage of ECGs. ECG parameters evaluated and captured in the study database will include RR, PR, QRS, and QT intervals as well as normal sinus rhythm. Any clinically significant ECG finding will be recorded as an AE. ECG recording will not be collected for subjects in the Non-Treatment concurrent control arm Part A (Part A Arm 2).

Laboratory and Endocrine Risks:
The semi-synthetic human ghrelin to be used in the clinical study is identical to human physiologic ghrelin. Under the original sponsor of the IND, this molecule was extensively characterized in both young adults and the older adult populations under 9 clinical studies and was found to be very safe. The information is summarized in the table above. Please note the additional PD biomarker marker data included that was not referenced in the Investigator Brochure. The longest duration study of the completed studies was ASBI307 in which 151 subjects were given one of two doses BID of OXE103 for 12 weeks at the same dose level as this study. The current study is substantially shorter at 14 days of treatment.

Subjects will undergo laboratory testing at Day 1 with a complete metabolic profile (CMP), to include liver function and glucose, and complete blood count (CBC). Significant abnormalities in serum creatinine (>2.5 mg/dL), or alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal, or bilirubin >2.5 mg/dL will exclude subjects from participation. Study team will collect CBC and CMP (with fasting glucose, fasting when possible) at visits 2 through 4 to monitor for any changes during treatment. If there are any clinically significant abnormal values that have not yet corrected, labs will be repeated at 7-day intervals until they normalize. Additional serum will be taken with each laboratory sample for correlative testing of sparse PK sampling and anti-ghrelin antibody and biomarker testing at study visits 1-5. Subjects enrolled in the Part A Arm 2 non-treatment control group will have these correlative lab samples taken at Days 1 and 15.

Outcomes & Study Tools:
Symptom reduction (AIM 1): Our primary goal is to describe the change in number of symptoms and/or severity in acute and sub-acute concussion with treatment with OXE-103 using the PCSS at Days 1 and 15. We will also collect data at Days 21 and 44 to potentially describe long term changes and potential lasting effect (AIM 4).

Subjects will complete the PCSS at the following timepoints[17]: upon signing consent (score must $\geq$20) (Day 1), as well as days 4, 8, 11, 15, 21 and 44. Subjects will be instructed to record their symptoms at the same time of day for each assessment timepoint. There can be a two-hour window either way. (e.g. 12PM +/- 2 hrs.). The PCSS is a self-reported assessment of 22 symptoms using a Likert-type scale ranging from 0-6, with 0 indicating no difficulty with the outlined symptom and ratings of 1-6 representing mild-to-severe difficulty with the symptom. The reliability and validity of the PCSS are well documented [18-20] We will also ask subjects to rank their 4 most burdensome symptoms (4MBS) at Day 1 and we will analyze these separately. As stated in the Specific Aims the purpose of this study is to collect data that would further refine clinical endpoints that could be used for larger Phase 2 studies and possibly lead to the establishment of pivotal endpoints for Phase 3 registration trials. The 22 symptom PCSS assessment is designed to cover the full spectrum of concussion related symptoms across cognitive, emotional and somatic domains. In that regard the PCSS is particularly useful for diagnosis and monitoring recovery of patients post injury. However, due to the number of symptoms across cognitive, emotive and somatic domains, resolution of several mild symptoms may result in a change in the overall symptom score with relatively minor clinical impact on the patient's well-being. Pre-IND feedback already obtained from the FDA has noted that an effective therapy for concussion must impact the way a patient feels or functions. By including a specific analysis of the patient perceived 4MBS we are likely to be able to correlate symptom scores with improvement in the quality of life tools also being used in the study. The completion of the PCSS will take an estimated 5 minutes.

Quality of Life (AIM 2): A secondary goal is to examine change in quality of life with treatment of acute and sub-acute concussion. We hypothesize that OXE-103 will reduce symptoms when comparing days 1 and 15 and therefore improve quality of life as assessed by 1) Quality of Life after Brain Injury scale (QOLIBRI) and 2) a PGAS.

The QOLIBRI is a 37 item instrument specifically developed to assess health-related quality of life (HRQoL) of individuals after traumatic brain injury [21]. Since it was developed for TBI as a disease or condition-specific HRQoL instrument, it is expected to be more sensitive than generic quality of life tools. The QOLIBRI was developed by an international task force in two multi-language studies involving over 2000 persons after TBI. Use of a TBI-specific assessment of HRQoL can detect the effects of interventions by measuring physical, psychological, daily life and psychosocial changes typical of TBI. An increase/decrease of 20% in QOLIBRI is judged to represent an improvement.

In addition, a PGAS will be used in this study. The tool will utilize a visual analog scale (VAS) to simply assess the patient's global assessment of their symptoms via the question "How would you rate the effect of your symptoms on how you feel or function today?". Patients will be instructed to rate the effects of their symptoms from 0 to 10 (with 0 being no effect and 10 being worst effect). An increase/decrease of 20% in PGAS is considered to indicate improvement.

The QOL measures will be obtained on day 1, 4, 8, 11, 15, 21, & 44. The completion of these will take an estimated 15 minutes. The PGAS VAS will be obtained at all visits.

Cognitive testing (AIM 5): A secondary outcome measure is to summarize change in cognitive function in the 2 groups. We hypothesize that the mechanism of action of OXE-103 will allow an improvement in cognitive function.

Subjects will complete computerized neurocognitive testing on an iPad using BrainCheck [22] BrainCheck is a validated digital assessment tool to aid in the diagnosis of mild cognitive decline. The tool measures a battery of 7 tests to measure cognition, reaction time, and balance. BrainCheck is a Computerized Cognitive Assessment Aid, a device that provides an impression of a person's current level of cognitive function. It is registered as a Class II medical device with the (FDA). (Registration number: 3014129043). Neurocognitive tests use small tasks to directly measure specific aspects of brain function. BrainCheck has created a library of neurocognitive assessments that measure specific components of brain function, such as reaction time, attention, visual processing and memory.
BrainCheck assessments include a coordination balance test measuring static and dynamic balance using the Ebbinghaus Illusion, a digit symbol substitution test for general cognitive performance, the Flanker test measuring visual attention, the Stroop Effect measuring reaction time, Trails A&B measuring visual attention and task switching and Recall tests to measure immediate and delayed memory. All scoring algorithms compare test results to a normative age matched dataset. All these tests are simple video games that require no special skills and are expected to cause no distress. The total time to complete the battery of tests is estimated to be 15 minutes. BrainCheck will be conducted on Days 1, 4, 8, 11, 15, 21, and 44. The iPads will be collected at the end of the subjects' study participation in all study procedures requiring use of an iPad. If a subject withdraws from the study, they will be asked to return the iPad to the study team.

Electronic PHI data will be kept on Amazon (HIPAA compliant) servers. The computers are all password protected. Server access is limited to study team and IT representatives, including any Amazon server representatives. Access to study specific data and communications relating

to the study will be limited to the PI and PI's staff, study personnel, responsible individuals from the study sponsor and appropriate regulatory agencies. The research data will not be added to the subject's medical records.
Amazon work servers (AWS) has an established information security organization managed by the AWS security team and is led by the AWS Chief Information Security Officer (CISO).

AWS meets criteria for security, availability, and confidentiality in the American Institute of Certified Public Accountants (AICPA) TSP Section 100, Trust Services Principles and Criteria for security, availability, processing, integrity, confidentiality, and privacy.

BrainCheck uses AWS HIPAA compliant services and holds third-party validations certifying that:
- AWS complies with the ISO 27017 implementation guidance of cloud-specific information security controls that supplement the ISO 27002 guidance and the ISO 27001 standard.
- AWS complies with the ISO 27001 internationally-recognized standard for security management best practices and comprehensive security controls following the ISO 27002 best practice guidance
- AWS complies with the ISO 27018 implementation guidance of controls applicable to public cloud personally identifiable information (PII) protection that supplement the ISO 27002 guidance and the ISO 27001 standard.

Information that will be transmitted from the app is limited to subject code, survey responses, and timestamps of survey responses. No location data will be transmitted. The vendor will not be permitted to attempt to re-identify subjects.

The iPads will be supplied by Oxeia Biopharmaceuticals.

ECG monitoring will be conducted via AliveCor's Kardiastation digital 6 lead ECG. Kardiastation has multiple 510(k) Class II device approvals through the FDA. Kardiostation is a Class II medical device cleared by the FDA for acquiring ECGs in the physician office. Kardiostation uses a HIPPA compliant smartphone app and cloud based database for storage of ECGs. ECG parameters evaluated and captured in the study database will include RR, PR, QRS, and QT intervals as well as normal sinus rhythm. Any clinically significant ECG findings will be recorded as an AE. All ECGs will be kept for the Clinical Trials File.

Statistical Analysis:
This pilot study will describe changes observed within Part A and Part B: placebo versus OXE-103. Since the study is exploratory, analysis will focus on descriptive comparative statistics and not on a prespecified 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 all Study Days 1, 4, 8, 11, 15, 21, and 44 will be analyzed.

The primary objective will be to determine the proportion of subjects (responders) who experience a clinically meaningful benefit as defined by a reduction of 20% in both the number and severity of concussion related symptoms. Concussion related symptoms will be measured using the 22 symptom PCSS. Severity of each of the 22 symptoms is graded by the patient on a 7-point Likert Scale. This scale has been used extensively to assess patients with concussion/mTBI[18, 19].

In addition, in order to control for the effect of changes in clinically minor symptoms on the overall number and severity of the PCSS, data will also be analyzed based on change of the

4MBS for each subject. This type of analysis has been employed in evaluation of patient reported outcomes for migraine and is discussed in an FDA guidance document (Dodick et al. 2018, Migraine 2018 FDA).

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.***" In order to correlate changes in symptom number/severity to effect on quality of life, two quality assessment tools will be used including QOLIBRI and a PGAS. Improvements in these assessments will be compared to definition of Responder to assess meaningful clinical improvements in response to treatment with OXE-103.

In addition, patient reported outcomes on the PCSS scale will be correlated with objective digital measures of cognition and balance/stability using BrainCheck a Class-II FDA device.

Medical history and test results will be housed in a REDCap.

Plans for Assuring Subjects' Privacy and Confidentiality

Signed consent forms and data forms will be stored in a designated file cabinet belonging to a member of the study team with limited access. Outcomes data will be entered into the aforementioned REDCap database and access will be restricted to staff members with approval. All analyzed data will be de-identified before submitting to the sponsor or scientific journals, etc. per HIPAA guidelines. Each participant will be assigned a unique study number to allow tracking of information over time. Personally-identifying information will be removed from initial data once a study number has been assigned, and from subsequent data once new data has been matched to an existing study number. The identity of participants and their associated study numbers will be housed in the Velos system, which will only be accessible by study team members who have authorization to access.

Follow-up

Subjects will be recruited from the CCM. These patients will continue with their standard care at the CCM upon completion of or removal from the study.

Study findings will be summarized and reported within the University of Kansas Medical Center (KUMC) and TUKHS (student research forum, seminars), in the community (aggregate data discussed in education or in-service forums), and professionally (conference proceedings, journal publications).

Record Retention Issues

The study team will retain any research and data records for 5 years in accordance with institution and federal requirements, as applicable. Records will be maintained in a secure method, with restricted or limited access to only authorized individuals. Records will be kept in a locked file cabinet inside a locked office.

Part A Study Design - Schedule of events
Arm 1 (OXE-103)

Assessment	Day						
	1	4	8 +/-1	11	15	21 +/-1	44 +/-3
Clinic Visit	1		2		3	4	5
Informed Consent	X						
Inclusion/ Exclusion Criteria	X						
Demographics	X						
Body Weight	X		X		X		X
Vital signs (temperature, heart rate, blood pressure)	X		X		X		X
Medical History, including current TBI injury, mental health diagnoses, and neurologic conditions (including any cognitive dysfunction)	X						
Adverse Effects	X	X	X	X	X	X	X
Prior Medications/Therapy Hx	X						
Physical Examination	X		X		X	X	X
Neurological Examination	X		X		X	X	X
Concomitant Medications	X		X		X	X	X
ECG	X		X		X	X	
Labs: serum/urine pregnancy test	X						
Labs: CMP & CBC[1]	X		X		X	X	
Labs: PK sampling, anti-ghrelin anti-body and biomarker	X		X		X	X	
Train subcutaneous injection	X						
PCSS	X	X	X	X	X	X	X
Ipad Neurocog and balance (BrainCheck)	X	X	X	X	X	X	X
QOL - QOLIBRI	X	X	X	X	X	X	X
QOL - PGAS VAS	X	X	X	X	X	X	X
PHQ-9	X		X		X		X
Administer OXE-103 40ug/kg OR placebo SC BID **	X Study Days 1-14						
Phone Only (no in-person required)		X		X			

[1]If there are any clinically significant abnormal values that have not yet corrected at Day 15, labs will be repeated at 7-day intervals until they normalize.

**Assessments and questionnaires performed and collected on Day 1 & 8 will be completed prior to dispensing of OXE-103.

Part A Study Design - Schedule of events
Arm 2 (Non-treatment concurrent control group)

Assessment	**Day**						
	1	**4**	**8 +/-1**	**11**	**15**	**21 +/-1**	**44 +/-3**
Clinic Visit	**1**				**2**		**3**
Remote Testing Only (No Visit)		**X**		**X**			
Remote Visit OR Clinic Visit			**X**			**X**	
Informed Consent	**X**						
Inclusion/ Exclusion Criteria	**X**						
Demographics	**X**						
Body Weight	**X**				**X**		**X**
Vital signs (temperature, heart rate, blood pressure)	**X**				**X**		**X**
Medical History, including current TBI injury, mental health diagnoses, and neurologic conditions (including any cognitive dysfunction)	**X**						
Prior Medications/Therapy Hx	**X**						
Physical Examination	**X**				**X**		**X**
Neurological Examination	**X**				**X**		**X**
Concomitant Medications	**X**				**X**		**X**
Labs: PK sampling, anti-ghrelin anti-body and biomarker	**X**				**X**		**X**
PCSS	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Ipad Neurocog and balance (BrainCheck)	**X**	**X**	**X**	**X**	**X**	**X**	**X**
QOL - QOLIBRI	**X**	**X**	**X**	**X**	**X**	**X**	**X**
QOL - PGAS VAS	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PHQ-9	**X**		**X**		**X**		**X**

Part B Study Design - Schedule of events
Arms 1 (OXE-103) and 2 (placebo)

Assessment	Day						
	1	4	8 +/-1	11	15	21 +/-1	44 +/-3
Clinic Visit	1		2		3	4	5
Informed Consent	X						
Inclusion/ Exclusion Criteria	X						
Demographics	X						
Body Weight	X		X		X		X
Vital signs (temperature, heart rate, blood pressure)	X		X		X		X
Medical History, including current TBI injury, mental health diagnoses, and neurologic conditions (including any cognitive dysfunction)	X						
Adverse Effects	X	X	X	X	X	X	X
Prior Medications/Therapy Hx	X						
Physical Examination	X		X		X	X	X
Neurological Examination	X		X		X	X	X
Concomitant Medications	X		X		X	X	X
ECG	X		X		X	X	
Labs: serum/urine pregnancy test	X						
Labs: CMP & CBC[1]	X		X		X	X	
Labs: PK sampling, anti-ghrelin anti-body and biomarker	X		X		X	X	X
Train subcutaneous injection	X						
PCSS	X	X	X	X	X	X	X
Ipad Neurocog and balance (BrainCheck)	X	X	X	X	X	X	X
QOL – QOLIBRI	X	X	X	X	X	X	X
QOL – PGAS VAS	X	X	X	X	X	X	X
PHQ-9	X		X		X		X
Administer OXE-103 40ug/kg OR placebo SC BID**	X **Study Days 1-14**						
Phone Only (no in-person required)		X		X			

[1]If there are any clinically significant abnormal values that have not yet corrected at Day 15, labs will be repeated at 7-day intervals until they normalize.

**Assessments and questionnaires performed and collected on Day 1 & 8 will be completed prior to dispensing of OXE-103.

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Appendix 1

A. Toxicology

Nonclinical toxicity studies of OXE103 (SUN11031) have been conducted by SC and IV administration to mice, rats, rabbits and monkeys. Single dose toxicity studies were conducted in rats (SC and IV) and monkeys (IV) and repeat-dose toxicity studies were conducted in rats, rabbits and monkeys following either SC or IV administration. No deaths or moribund sacrifice were reported following SC (26-week administration in rats with doses up to 20,000 µg/kg and 39 week administration in monkeys with doses up to 5000 µg/kg) or IV (4- and 13-week administration in rats with doses up to 100,000 and 25,000 µg/kg, respectively, and 4- and 13-week administration in monkeys with doses up to 30,000 and 3000 µg/kg, respectively) administration. The monkey is considered to be the most sensitive species.

In the 26-week toxicity study (0; 3000; 7000; 20,000 µg/kg/day) evaluating OXE103 (SUN11031) SC administration in rats, no animals in any group died and the 3000 µg/kg/day dose in males was well tolerated, with no toxic signs observed. An increase in urinary β2-microglobulin (β2-MG) and a decrease in serum albumin, albumin ratio and albumin/globulin (A/G) were noted in females at 3000 µg/kg or more, an increase in urinary β2-MG in males and a decrease in serum total protein in females at 7000 µg/kg or more, and an increase in urinary albumin, decreases in albumin ratio and A/G in serum in males at 20,000 µg/kg. These were slight toxicological changes. The NOAEL was determined to be 3000 µg/kg/day for males and less than 3000 µg/kg/day for females.

In the 39-week toxicity study (0; 300; 1000; 5000 µg/kg/day) evaluating OXE103 (SUN11031) SC administration in monkeys, no animals died, and doses up to 1000 µg/kg/day were well tolerated with no toxic signs observed. Local irritation was observed at the injection site and considered to be related to the dosing procedure and the vehicle (0.03 mol/L acetic acid buffer [pH 4.0] containing 10% sucrose and 1% benzyl alcohol). Antibody titers were below the lower limit of detection. However, incidences and/or grades of inflammation of the subcutaneous tissue and regeneration of the cutaneous muscle fiber were slightly greater in the 5000 µg/kg group than in the vehicle control group. The NOAEL was determined to be 1000 µg/kg/day.

Male and female rats treated with OXE103 (SUN11031) by SC administration for 13 weeks developed anti OXE103 antibody at the end of the dosing period which did not differ from control rats at the end of the recovery period.

No effects were observed on fertility in rats, on reproductive function in parental rats and maternal rabbits, or on embryo-fetal development in rats or rabbits by IV administration. In addition, no effects were observed on maternal rabbits and on embryo-fetal development in rabbits by SC administration. In an IV-dose study on pre- and postnatal development including maternal function in rats, a tendency to increase in body weights of live newborns

was noted at 300 µg/kg/day or more as pharmacological effects of OXE103 (SUN11031).

OXE103 (SUN11031) was not judged to be genotoxic. Although some results suggest that OXE103 may promote proliferation of selected cell types under experimental conditions, there is no clear evidence of tumor promoting potential in vivo.

In monkeys, a dose of 1000 µg/kg is approximately 4 fold higher than a clinical dose of 40 µg/kg twice daily based on body surface area. This may also be expressed as a systemic equivalent total daily exposure of approximately 28- and 12 fold for maximum plasma concentration (Cmax) and area under the plasma concentration time curve (AUC), respectively.

B. Clinical Overview

Safety, tolerability and pharmacokinetics of, SUN11031 (alternatively OXE103) has been evaluated in 9 clinical studies with the SC and IV routes of administration:

- 4 phase 1 clinical studies in healthy volunteers:
  - 3 in Japan (NA 1401, NA 1501, and NA 1502 – all IV administration) and
  - 1 in the US (ASBI 301 – SC and IV administration).
- 4 phase 2 clinical studies:
  - 1 study in subjects with eating disorders conducted in Japan (NA 2601 – IV administration),
  - 1 study in subjects with cachexia associated with CHF conducted in Poland (ASBI 303 – SC administration),
  - 1 study in subjects with cachexia associated with COPD conducted in the US (ASBI 304 – SC administration), and
  - 1 multinational study in subjects with cachexia associated with COPD (ASBI 307 – SC administration).
- 1 phase 3 clinical study:
  - in subjects with eating disorders in Japan (NA 3801 – IV administration).

SUN11031 has been administered as either an IV bolus or IV infusion in 6 clinical studies (NA 1401, NA 1501, NA1502, ASBI 301, NA 2601, and NA 3801) and as an SC injection in 4 clinical studies (ASBI 301, ASBI 303, ASBI 304, and ASBI 307).

Subcutaneous injections of SUN11031 at doses up to 45.5 µg/kg once daily and 22.7 µg/kg bid for up to 7 days, have been administered to healthy subjects. Subcutaneous doses of SUN11031 10 µg/kg bid have been administered to subjects with cachexia associated with CHF (ASBI 303; 6 subjects; up to 14 days) and up to 20 µg/kg bid have been administered to subjects with cachexia associated with COPD (ASBI 304 [during which 9 subjects were administered 10 µg/kg bid and 8 subjects were administered 20 µg/kg bid] for up to 21 days and ASBI 307 [during which a total of 75 and 76 subjects were administered 20 and 40 µg/kg bid SUN11031, respectively]) for up to 3 months.