ENTHEON

PROTOCOL TITLE:	Evaluation of the effect of Ketamine on neurological activity as measured by quantitative EEG
PROTOCOL NUMBER:	EBIQ-101
Protocol Date:	13 October 2021
Protocol version:	Version 4.0
STUDY PHASE:	Open Label, Observational
Sponsor:	Entheon Biomedical Corp., 595 Howe St. 10th floor, Vancouver, BC, V6C 2T5, Canada

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Protocol Approval Page

Protocol Number EBIQ-101

Evaluation of the effect of Ketamine on neurological activity as measured by quantitative EEG

Study Sponsor

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Oct 13, 2021

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Investigator's Agreement

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I have read this protocol and agree to conduct the observational study as outlined herein. I will ensure all study staff members have read and understand all aspects of this protocol. I agree to fully cooperate with Entheon Biomedical and their agents. I will adhere to all applicable regulations and guidelines regarding observational studies during and after the study completion,

Tyson Lippe

Signature of Site Investigator

10/13/2021

Date

Tyson Lippe

Print Name

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List of Abbreviations and Definitions

10-20 system	International 10-20 system describing the location of scalp electrodes. 10 and 20 refer to 10% and 20% of the total front-back or right-left distance of the skull
AE	Adverse Event
C4A and C4B genes	C4A and C4B genes are situated withing the Major Histocompatability Complex (MHC) gene locus. C4A mediates neuronal pruning and synapse elimination during postnatal brain development. C4B gene favours binding to carbohydrate surfaces. Higher C4A is associated with schizophrenia vulnerability.
CADSS-6	Clinician Administered Dissociative Symptom Scale. The CADSS-6 is a shorter form developed for easier clinical use of the 23-item CADSS. There are 5 options for each question: 0=not at all; 1=Mild; 2=Moderate; 3=Severe; 4=Extreme.
CNS	Central Nervous System
COMT gene	COMT Gene provides instructions to make the Catechol-O-MethylTransferase enzyme.
CRA	Clinical Research Associate
CRF	Case Report Form
CYP2B6 gene	CYP2B6 gene encodes the Cytochrome P450 class of metabolic enzymes found mainly in the human liver. It metabolizes ketamine, controlling how fast ketamine is eliminated from the body.
DISC1 gene	Disrupted in Schizophrenia 1 genotype. Well established as a genetic risk factor across a spectrum of psychiatric disorders. DISC1 is highly expressed during critical brain development periods.
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EEG	Electroencephalogram
Electrode	Conductor through with electricity enters or leaves
Endophenotype	A quantitative biological trait that is reliable in reflecting the function of a discrete biological system and it is reasonably heritable. It is also known as an intermediate phenotype. It is more closely related to the root cause of a disease than a broad, clinical phenotype.

GCP	Good Clinical Practice. This is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trials participants are protected.
HAM-D	Hamilton Depression Rating Scale. Widely used clinician-administered depression assessment scale.
HIPAA	Health Insurance Portability and Accountability Act
HPA Axis	Hypothalamic-Pituitary-Adrenal axis – central stress response system
HTR2A gene	HTR2A serotonin gene influences the serotonin 5-HT2A receptor pathway
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. This is an international body that sets guidelines for clinical research.
ICMJE	International Committee of Medical Journal Editors. A group of general medical journal editors and representatives of selected related organizations working together to improve the quality of medical science and its reporting.
IRB	Institutional Review Board. This is an independent body constituted of medical, scientific, and non-scientific member whose responsibility is to ensure the protection of the rights, safety and well-being of human participants involved in a clinical trial. Also known as the ethics committee.
Ketamine	Belongs to a class of drugs known as dissociative anesthetics. It is a noncompetitive NMDAR antagonist.
MDD	Major Depressive Disorder
Met/Met COMT gene	Slow variation of the COMT gene associated with greater levels of cortisol and HPA axis dysfunction
NMDA	N-Methyl-D-aspartate
NMDAR	N-Methyl-D-aspartate receptor. It is a glutamate-gated cation channel critical for development of Central Nervous System (CNS) and neuroplasticity.
NRG1 gene	Neuregulin 1 gene stimulates cell proliferation and differentiation, including neurite output and myelin production. Over expression results in disrupted excitatory-inhibitory connections, reduced synaptic plasticity and abnormal

	dentritic spine growth. Under expression is linked to various autoimmune disorders.
PMQ-SF	Psychedelic Music Questionnaire Short Form. The PMQ-SF assess the impact of music on patients receive Ketamine for treatment resistant depression. It looks at measures of mood, anxiety, suicidality and psychological/physical pain through the rating of 15 statements and then 2 free answer questions.
PTSD	Post-Traumatic Stress Disorder
QIDS-SR 16	The Quick Inventory of Depressive Symptomatology- Self Report. The QIDS-SR 16 is derived from the 30-item Inventory of Depressive Symptomatology (IDS). It has 16 items that assess nine DSM-IV diagnostic symptom domains: sad mood, poor concentration, self-criticism, suicidal ideation, anhedonia, energy/fatigue, sleep disturbance, decrease/increase in appetite/weight, and psychomotor agitation/retardation
SAE	Serious Adverse Event defined as an adverse event that either: causes death; is life-threatening; causes hospitalization or prolongs existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect
SOC	Standard of Care

1. Introduction

1.1 Rationale

This observational study will allow data to be collected to demonstrate changes in brain activity following administration of standard of care (SOC) Ketamine. By comparing genetic markers across participants, data on impact of genetic markers and response to Ketamine will also be analysed. This data will contribute to the design of future studies utilizing Ketamine for various psychiatric disorders. This study will focus on treatment-resistant Major Depressive Disorder (MDD).

1.2 Background

Ketamine traditionally has been used as an anesthetic. It is a NMDA receptor antagonist which has rapid and potent antidepressant effects in treatment-resistant Major Depressive Disorder and Bipolar Depression. Ketamine treatment is used for hard-to-treat depression, post-traumatic stress disorder (PTSD) and other psychiatric disorders. These disorders are accompanied by abnormal brain activity with emotional alteration. Ketamine has widespread effects on brain activity of individuals who are resistant to other treatments for psychiatric disorders such as anxiety, PTSD and depression (Blanke, 2009; Iadarola, 2016).

Electroencephalogram (EEG) is a test used to record electrical activity in the brain. Brain cells communicate utilizing electrical impulses. The EEG uses electrodes on the scalp to measure the brain wave patterns and records them. The EEG is a safe procedure having been used for many years, causing no discomfort to the participant. The electrodes record brain activity but do not produce any sensation and there is minimal risk of getting an electric shock as there is no current being directly delivered to the participant. EEG has high temporal specificity with an ability to pinpoint the exact source, making it an excellent tool for this clinical study (Hubbard, 2019).

Conventionally, a wet electrode EEG system is utilized. Wet electrodes rely on conductive gel to record the brain waves. They are messier to use and require a trained EEG technician for application. Dry electrode EEG systems have up to 20 conductive pins per electrode and the pins are coated with either silver, gold or nickel. The dry electrodes do not need any gel application which makes it easier to apply and do not require as much training. This study proposes to utilize Zeto EEG system, a dry, wireless system.

Previous research has linked prefrontal EEG patterns to Ketamine effects in patients with diagnosed treatment-resistant depression (Cao, 2019). Genetic markers may play a role in the brain reactions to Ketamine. Several EEG parameters are potential endophenotypes when looking at different psychiatric disorders (Malone 2014). Researchers utilized cheek swabs to assess which markers contributed most to a decrease in absolute HAM-D scores and determined the ‘Met/Met’ variant of the COMT gene was the best genetic predictor of treatment outcome (Spronk 2010).

There are inter-individual genetic variations to psychedelic drug effects. Testing for specific genetic markers helps determine the effects expected. This study will look at the following five genetic markers:

- HTR2A
- CYP2B6 gene
- C4A and C4B genes
- NRG1 gene
- DISC1 gene

This observational study will observe genetic markers and EEG patterns from pre, during and post Ketamine administration.

2. Objectives and Purpose

The objective of this observational study is to determine the effects of routine, intramuscular, clinically administered Ketamine on the brain's electrical activity and biomarkers. The brain activity will be measured with an EEG electrode cap and the biomarkers will be collected via a cheek swab.

2.1 Primary Objective

The primary objective is to study what baseline EEG measures and genetic markers predict a Ketamine treatment response among participants with treatment-resistant Major Depressive Disorder.

2.2 Secondary Objectives

The secondary objectives are to:

- Evaluate neurological changes during Ketamine sessions via EEG
- Evaluate persistent neurological changes in a follow up session post-treatment
- Identify biomarkers based on neurological changes during Ketamine sessions via cheek swab

3. Study Description

This is an Open Label Observational Study with the primary objective to assess brain activity in patients prior to, during and after Ketamine treatment and to assess genetic markers prior to Ketamine treatment. This is a non-interventional study that will observe the EEG pattern of participants who, per standard of care, are treated with intramuscular Ketamine. The administration of the Ketamine during this study is not considered investigational. The experimental intervention, measurements via EEG, will be offered to patients of the study

site presenting for intramuscular (IM) ketamine treatment per the site's established and evidence-based protocol as part of their regular clinical care. Participants in this study have already been determined to have a medically appropriate indication for IM Ketamine treatment, independent of enrollment in this study. Given the requirement, per study protocol, to wear an EEG headset, permit a video recording of the session and complete study measures, participants will be compensated by having treatment costs paid by the study sponsor.

There will be 36 participants enrolled.

4. Scheduling of Visits

All visits will occur at the clinic of the principal site investigator. The study will enrol for approximately 3-4 months. All times should be recorded using the 24-hour clock.

4.1 Discontinuation or Participant Withdrawal

Participants may withdraw at any time from the study under the following circumstances:

- Withdrawal of informed consent
- Lost to follow-up
- Serious adverse event occurs
- In the opinion of the investigator, the participant should be withdrawn

5. Study Population

5.1 Inclusion Criteria

1. Primary DSM-V diagnosis of treatment-resistant Major Depressive Disorder (may have secondary diagnoses of general anxiety, substance disorder)
    - Non-responders to at least 2 previous anti-depressant medications prescribed by a physician in the past five years
    - Score of ≥20 on Montgomery-Asberg Depression Rating Scale (MADRS) (i.e., moderate to severe depression)
2. All genders aged 21 to 60 years of age
3. Prescribed Ketamine or currently being treated with Ketamine for treatment-resistant Major Depressive Disorder
4. Willing to wear an EEG headset and an eye mask
5. Willing to permit a digital video recording to be collected for safety monitoring
6. Willing to listen to ambient sound
7. Willing to have a genetic cheek swab

5.2 Exclusion Criteria

1. Pregnancy
2. Traumatic Brain Injury within past 3 months
3. Body weight < 50 kg or > 120 kg
4. Coronary heart disease
5. Uncontrolled hypertension as defined in the ACC/AHA Hypertension Guidelines
6. Previous contact with Ketamine (therapeutically or recreationally) outside of treatment at the study site
7. Primary psychotic disorder (e.g., schizophrenia, schizoaffective disorder)
8. Bipolar disorder with current manic, hypomanic or mixed state
9. Post-traumatic stress disorder
10. Obsessive-compulsive disorder
11. Primary substance-use disorder
12. Alcohol consumption 24 hours prior and 48 hours subsequent to treatment
13. Currently using any of the following medications:
    - Benzodiazepines for 6 hours prior to treatment and 2 hours after treatment
    - Lamotrigine for 6 hours prior to treatment
    - Amphetamine-based stimulants for 6 hours prior to treatment
    - MAO-Is may be taken but blood pressure must be monitored

6. Study Procedures

	Screen V1	V2	V3-V11	V12
	Day 0	Day 1 (±1 day) Session 1	Days 3, 5, 8, 11, 18, 25, 32, 46, 67 (±2 days) Sessions 2-10	Day 74 ± 2 days
Eligibility criteria	X			
Informed Consent	X			
Medical History and current medical conditions	X			
Urine HCG Pregnancy Test	X			
Demography	X			
Cheek Swab[1]		X		
Questionnaires[2] (CADSS-6, QIDS-SR-16, PMQ-SF)		X	X[2]	X
EEG applied[3]		X	X	
EEG measured 5 ±2 min eyes closed/ 5 ±2 min eyes open prior to session		X	X	X
Wavepaths music track played		X	X	
EEG recording prior to injection and through to 15 minutes after end of session[3]		X	X	
Ketamine Injection (SOC) [4]		X	X	
Adverse Events		X	X	X
Concomitant Medications	X	X	X	X

[1] Cheek swab for testing of genetic markers and questionnaires are done directly prior to the first session beginning.
[2] Questionnaires to be administered at first and last sessions as well as at day 74 only for a total of 3 times each
[3]Sessions are approximately 60 minutes in duration, EEG is continuous for approximately 75 minutes. A digital video recording will be collected at each visit for safety monitoring.
[4] There are a total of 10 sessions per participant over a span of 67 days

6.1 Questionnaires

Several trait- and state-related questionnaires will be administered at the beginning of the first and last session. Each questionnaire will be given on 2 occasions:

6.1.1 Clinician Administered Dissociative Symptom Scale (CADSS-6; Rodrigues, 2021)

The CADSS-6 is a shorter form developed for easier clinical use of the 23-item CADSS (Bremner, 1998). There are 5 options for each question: 0=not at all; 1=Mild; 2=Moderate; 3=Severe; 4=Extreme. The 6 questions are presented in 3 areas:

1. Derealization
2. Depersonalization
3. Amnesia

6.1.2 The Quick Inventory of Depressive Symptomatology (QIDS-SR 16; Rush, 2000, Rush, 2003)

The QIDS-SR 16 is derived from the 30-item Inventory of Depressive Symptomatology (IDS). This self-report version will be utilized in the study. It has 16 items that assess nine DSM-IV diagnostic symptom domains: sad mood, poor concentration, self-criticism, suicidal ideation, anhedonia, energy/fatigue, sleep disturbance, decrease/increase in appetite/weight, and psychomotor agitation/retardation.

6.1.3 Psychedelic Music Questionnaire Short Form (PMQ-SF; Douglas Mental Health University Institute, 2021)

The PMQ-SF assess the impact of music on patients receive Ketamine for treatment resistant depression. It looks at measures of mood, anxiety, suicidality and psychological/physical pain through the rating of 15 statements and then 2 free answer questions. Music is believed to improve Ketamine tolerability.

6.2 Wavepaths Music Tract

A music track will be played during the sessions only for individuals in this research study. This music track is from Wavepaths Ltd and will be started after the baseline EEG measurements are taken but prior to the Ketamine administration. The music played is very uniform in tone throughout the session but there is no repetition in the tract. It will be played with dedicated speakers in the session room.

6.3 Screening Visit 1 (Day 0)

Before a participant is enrolled, and prior to any evaluations, the investigator or designee must explain the study in sufficient detail to allow for an informed decision to participate. Proper participant preparation is essential for participant comfort during the Ketamine treatment and will be discussed with each participant.

Once informed consent is obtained, the following evaluations will occur:

- Demography collected
- Medical history collected
- Current medical conditions collected, along with medications
- Eligibility criteria reviewed

Once complete, the first session will be booked for the next day (±1 day).

6.4 Visit 2 (Day 1, ± 1 day), Session 1

The following evaluations are conducted prior to the session beginning:

- Cheek swab
- Administration of questionnaires (CADSS-6, QIDS-SR-16, PMQ-SF)
- Administration of EEG
- EEG measurements taken prior to Ketamine administration
    - 5 ±2 minutes with eyes closed
    - 5 ±2 minutes with eyes open
- Start the music track

The following evaluations are conducted during and after Ketamine administration:

- Ketamine administered intramuscularly, as per the usual clinical care
- EEG measurements taken throughout 60-minute session and completed 15 ±2 minutes after end of session (e.g., at end of 75 minutes of continuous EEG)
- Digital video recording will be collected for safety monitoring

6.5 Visit 3 to Visit 10 (Days 3, 5, 8, 11, 18, 25, 32, 46, ± 2 days), Sessions 2 to 9

- Administration of EEG
- EEG measurements taken prior to Ketamine administration
    - 5 ±2 minutes with eyes closed
    - 5 ±2 minutes with eyes open
- Start the music track
- Ketamine administered intramuscularly, as per the usual clinical care
- EEG measurements taken throughout 60-minute session and completes 15 ±2 minutes after end of session (e.g., at end of 75 minutes of continuous EEG)
- Digital video recording will be collected for safety monitoring

6.6 Visit 11 (Day 67, ± 2 days) Session 10

- Administration of questionnaires (CADSS-6, QIDS-SR-16, PMQ-SF)
- EEG measurements taken prior to Ketamine administration
    - 5 ±2 minutes with eyes closed
    - 5 ±2 minutes with eyes open

- Start the music track
- Ketamine administered intramuscularly, as per the usual clinical care
- EEG measurements taken throughout 60-minute session and completes 15 ±2 minutes after end of session (e.g., at end of 75 minutes of continuous EEG)
- Digital video recording will be collected for safety monitoring

6.7 Visit 12 (Day 74, ± 2 days) Session 11

- Administration of questionnaires (CADSS-6, QIDS-SR-16, PMQ-SF)
- Start the music track
- Administration of EEG
    - EEG measurements taken
        - 5 ±2 minutes with eyes closed
        - 5 ±2 minutes with eyes open

Start the music track

7. Study Materials

The Zeto EEG system is dry, wireless and battery powered. It has 10-20 compliant montage, up to 250 Hz bandwidth, and wireless recording and updating to cloud-based storage with a real time cloud-based monitoring and analysis system. These features allow data to be streamed and accessed in real-time, a critical feature permitting simultaneous remote viewing and analysis. Zeto EEG is HIPAA compliant with the cloud platform for gathering data. A digital video recording will be collected during each session for safety monitoring.

Between each two recording sessions, it is recommended by Zeto that the electrodes attached to the headset be replaced to avoid signal quality deterioration from repeated use of the one-time electrodes and reduce risk of COVID and other viral / bacterial infections.

A music track will be played during the sessions only for individuals in this research study. This music track is provided by Wavepaths Ltd and will be started after the baseline EEG measurements are taken but prior to the Ketamine administration. It is a uniform tone throughout the session, but is not repeated and will be played on dedicated speakers positioned in the session room.

The cheek swab will be collected using swabs with cotton, foam or flocked tips. The coordinator will wear gloves and a surgical mask and will transfer the samples into dry transport tubes. The samples will be stored in the provided collection shipping envelope. These samples can be stored for up to 30 days at room temperature. If sent within 7-14 days of collection, they will be stored at room temperature. If the samples are potentially to be stored for longer, they will be put into a 4°C (40°F) refrigerator. The samples will be sent via postal service in the stamped

collection envelope provided, approximately weekly or by-weekly by the study staff to the HaluGen Life Sciences analysis laboratory located in Ontario Canada.

7.1 Packaging, Labelling and Storage

The EEG device will be stored in a locked area between uses. device will be utilized for all participants. After each use, the device will be cleaned appropriately, as per manufacturer's instructions. Between each two recording sessions, the electrodes attached to the headset will be replaced. At the end of the study, the device will be returned to Entheon Biomedical Corp.

7.2 Administration

EEG technologists from Zeto Inc. will train the site staff on the use of the device.

8. Warnings, Precautions and Contraindications

EEG is a safe procedure that has been used for many years. The test causes no discomfort to the participant. The electrodes record brain activity but do not produce any sensation and there is minimal risk of getting an electric shock as there is no current being directly delivered to the participant. Using the gel-free version is less stressful for the participant.

9. Assessment of Safety

This is a non-interventional study. Adverse events to be reported will be those related to the administration of the EEG device, not the Ketamine as it is being used as per standard of care. Participants will be observed for the entire time of their treatment. A nurse will check in on the participant regularly to minimize adverse events from occurring. The digital video recording can be viewed from outside the room to ensure safety.

The investigator is responsible for recording and reporting all adverse events observed or reported during the study from informed consent signature until the date of completion or discontinuation.

9.1 Definitions

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant during a clinical study, regardless of the causal relationship. All AEs that occur during the Ketamine administration will be collected in the study documentation. Only AEs that occur during the EEG administration will be reported in the case report forms.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence in a participant during a clinical study defined as:

- Resulting in death
- Life-threatening
- Requiring inpatient hospitalization or prolongation of existing hospitalization
- Resulting in permanent or significant disability/incapacity

- Resulting in congenital anomaly/birth defect

All SAEs will be reported by the investigator to the sponsor within 24 hours and to the IRB, as per their reporting guidelines. Note that SAEs are not necessarily causally associated with the study. All SAEs will be monitored by the sponsor.

10. Data Management and Study Assessments

This study is open label and observational, therefore it has inherent limitations. There is limited control over participant assessments as the treatment is per standard of care. The strength of this design is that it reflects daily clinical practice more closely than randomized controlled studies. Real-life observational data is essential to improve clinical practice worldwide.

The trained investigator staff will enter the data required by the protocol into the case report forms (CRFs) from source documents. A Clinical Research Associate (CRA) will review the CRFs and source documents for data discrepancies and issue queries. The CRA is responsible for checking the quality of data and ensuring that the investigative site is adhering to the study protocol. Source data verification is an essential part of the monitoring process, and the Investigator must grant direct access to the participant's source data.

10.1 Sample Size Considerations

The objective of the study is to assess baseline brain activity and genetic markers and secondarily to measure neurological changes during Ketamine sessions. This is an open-label, observational study to determine the feasibility of these measurements. The intent is to enrol 36 participants which should have the precision needed to observe and compare EEG activity pre, during and post Ketamine administration.

10.2 Data Analysis

The information will be summarized using description statistics (mean, median, standard deviation, minimum, maximum) for quantitative variables (e.g., cheek swabs, EEG data), and counts and percentages for categorical variables (e.g., gender).

10.3 Outcome Measures

The Primary Outcome Measure is the inter and intra patient variability in neurological activity.

The Secondary Outcomes are:

1. Correlation of neurological phenotypes with genetic markers
2. Correlation of neurological phenotypes of Clinician Administered Dissociative Symptom Scale (CADSS-6).
3. Correlation of neurological phenotypes of depressed patients with Quick Inventory of Depressive Symptomatology (QIDS SR-16)

4. Correlation of neurological phenotypes Psychedelic Music Questionnaire Short Form (PMQ-SF)

11. Administrative Procedures and Ethical Considerations

11.1 Ethical Conduct of Study

The study will be conducted in compliance with the Institutional Review Board (IRB) and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. To ensure the study conduct is according to the principles above, an audit may occur at any time by the sponsor, sponsor's designee or other representatives. The Investigator must agree to the audit of study-related records when requested.

All participants will sign a Health Insurance Portability and Accountability Act (HIPAA)-compliant consent form.

11.2 Medical Care

All participants will be informed that their right to medical care will not be affected in any way by their agreement or refusal to participate in this study and that they are free to withdraw from the study at any time without compromising their relationship with their clinician.

11.3 Participant Information and Informed Consent

Information in simple terms will be provided to explain the risks and the benefits of the participant's participation in the study, the procedures involved and other relevant details. Written informed consent must be obtained from the participant by the investigator (or designee) before the participant takes part in the study or before altering the medical regimen of the participant for the purpose of enrolling the participant in the study. The investigator must adopt a standardized approach for obtaining informed consent from each participant. Any anticipated circumstances under which the participant's participation may be terminated by the investigator without the need of the participant's consent.

Should the investigator decide to modify the Informed Consent document, the modified version must be approved by the sponsor or designee prior to its submission to the IRB. Should the IRB request modifications, the IRB's version must be submitted to the sponsor or designee for approval prior to study initiation. The original signed Informed Consent document is to be maintained with the source documents. The participant should receive a copy of the signed Informed Consent document. All signed and dated Informed Consent documents will be inspected by the CRA or designee.

11.4 Ethics Committee Review

Before study initiation, the investigator and institution must have written and dated approval from the Institutional Review Board (IRB) for the study protocol/amendment(s), written informed consent form (ICF), any consent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects. Appropriate reports on the progress of the study will be made to the IRB and the sponsor by the investigator in accordance with applicable regulatory regulations. When necessary, an extension or renewal of the IRB approval must be obtained, and copy forwarded to the sponsor. Upon approval and before the study start, the following IRB approval documentation must be sent to the sponsor.

- A letter documenting the IRB approval of the protocol and the ICF (indicating its title, protocol number and version).
- A letter documenting the IRB approval of amendment(s) to the protocol and/or the ICF, if applicable (indicating its title, protocol number and version).
- A list of the IRB members, their representative capacities, and their affiliations. Should this list be unavailable due to local regulations of the institution, a letter to this effect must be provided to the sponsor with a copy remaining in the study file.

The ICH guidelines for GCP specify that the committee should include persons of varying backgrounds (including peers of the responsible investigator and lay people) and must exclude the responsible investigator as a voting member.

11.5 Investigator Responsibilities

The investigator will perform the study as per the written protocol and ICH guidelines. It is the investigator's responsibility to ensure adequate time and appropriate resources are available prior to commitment. The investigator should also demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period.

The investigator will maintain a list of qualified persons to whom they have delegated significant study-related tasks (the Delegation of Authority Form). An up-to-date curriculum vitae for the investigator and sub-investigator must be provided to the sponsor prior to starting the study.

The investigator must adhere to the written protocol and enrol only those participants who have met protocol eligibility criteria. The investigator will sign an investigator's agreement to confirm acceptance and willingness to comply with the study protocol.

The investigator must communicate with the IRB to ensure accurate and timely information is provided during the study. Appropriate approvals must be in place prior to recruitment. Notification of any SAEs during the study must take place and

the IRB must be informed of study completion. The reason for any deviation from the protocol, including deviations from the visit schedule, must be documented.

The investigator must maintain adequate and accurate clinical trial documentation to ensure protocol procedures were adequately performed and provide documentation that study data was appropriately collected and accurately entered into the Case Report Form (CRF). The investigator will ensure all study files are maintained, including the IRB approved protocol and any amendments. The study monitor will confirm this is being done correctly.

12. Publication Policy

Entheon Biomedical Corp. is committed to ensure that publications of all its clinical study results in biomedical journals are done in a timely manner, regardless of the results. Publications should follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals (http://www.icmje.org). Entheon Biomedical Corp. is committed to ensuring that authorship for all publications comply with the criteria defined by the ICMJE.

The Investigator shall not publish any data (poster, abstract, paper, etc.) without advanced written authorization from the Sponsor.

13. References

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