UNIVERSITY OF CALIFORNIA, SAN DIEGO
HUMAN RESEARCH PROTECTIONS PROGRAM

TO: Dr. Doris Trauner
RE: Project #181455
A double-blind, crossover trial of cannabidiol to treat severe behavior problems in children with autism

Dear Dr. Trauner:

The above-referenced project was reviewed and approved by one of this institution's Institutional Review Boards in accordance with the requirements of the Code of Federal Regulations on the Protection of Human Subjects (45 CFR 46 and 21 CFR 50 and 56), including its relevant Subparts. This approval, based on the degree of risk, is for 365 days from the date of **IRB review and approval** unless otherwise stated in this letter. The regulations require that continuing review be conducted on or before the 1-year anniversary date of the IRB approval, even though the research activity may not begin until some time after the IRB has given approval.

Based on the information provided by the PI, the Committee concurs that the use of Epidiolex (EPX) in this project is exempt from the requirements of 21 CFR 312 under 21 CFR 312.2(b)(1), which indicates "the clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply: (i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug; (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product; (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product; (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and (v) The investigation is conducted in compliance with the requirements of 312.7.

Waiver of documented written consent has been granted for the screening portion of this project. The IRB under CFR 46.117(c)(2) waives the requirement for the PI to obtain signed consent because this research presents no more than minimal risk of harm to the subjects and involves no procedures for which written consent is normally required outside of the research context.

The IRB has reviewed this protocol in accordance with the guidelines on research involving children as research subjects and has found that this project meets the requirements as stated in 45 CFR 46.405 and 21 CFR 50.52 in that the research presents more than minimal risk; the research is justified by the anticipated benefits to the subjects; the relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches; and adequate provisions exist for soliciting the permission of the parents or guardians, and criteria for waiver of assent have been met as set forth in HHS regulations at 45 CFR 46.408 and 21 CFR 55 in that the capability of some or all of the children is so limited that they cannot reasonably be consulted.

The IRB determined that this project presents more than minimal risk to human subjects in that the probability and magnitude of harm or discomfort anticipated in the research are greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Date of IRB review and approval: **04/04/2021**

On behalf of the UCSD Institutional Review Boards,

/ag

Kip Kantelo
Director
UCSD Human Research Protections Program
858-246-HRPP (858-246-4777); hrpp@ucsd.edu

cc: CCR

Note: IRB approval does not constitute funding **or other institutional required approvals.** Should your studies involve other review committees such as Office of Clinical Trials Administration (OCTA), Office of Coverage Analysis Administration (OCAA), Conflict of Interest (COI), Protocol Review Monitoring Committee (PRMC), and committees under Environmental Health & Safety (EH&S) such as Institutional Biosafety Committee (IBC), Human Exposure Committee (HERC), and RSSC (Radiation Safety and Surveillance Committee), it is the researchers responsibility to ensure that all approvals are in place prior to conducting research involving human subjects or their related specimens.

Approval release date: 3/8/2021

UCSD HUMAN RESEARCH PROTECTIONS PROGRAM

GENERAL APPROVAL INFORMATION

The information below does not encompass all human subjects protections requirements, however, is intended to highlight those of significance to ensure awareness by researchers engaged in research involving human subjects or their related specimens and data.

Approval Letters and Consent Documents

Unless otherwise stated, approval letters will be accompanied by stamped, approved consents. Should a study be closed to accrual and no consent released as a result, this information will be documented on the approval letter. Also, any waivers will be documented in the approval letter (such as waiver of documented consent or waiver of authorization for use of PHI).

The PI must ensure approval is in place from other appropriate review boards (such as Radiation Safety, Institutional Biosafety Committee, Conflict of Interest, ESCRO, etc.)

If other institutions are involved, the PI must ensure that IRB approvals (or other administrative approvals) from those sites are secured and forwarded for the study file. In addition, PI's must ensure that the clinical trial agreement, as applicable, or other funding (such as a grant) is appropriately in place prior to conducting any research activities. IRB approval does not constitute funding approval.

Duration of IRB approval

The IRB may grant approval up to 365 days. (See 45 CFR 46.109(d) (DHHS) and 21 CFR 56.109(d) (FDA)). However, for some studies the IRB may grant approval for a lesser period or a specific number of subjects to allow for more frequent monitoring. The approval letter or related documentation will indicate this information.

Because IRB review of research studies must be completed at least annually, investigators should plan ahead to meet required continuing review dates. **Please submit complete continuing review documentation at least 45 days prior to the expiration date to guard against a lapse in IRB approval.** The signed continuing review facepages and any other required hard copies must be received by the HRPP office before the continuing review process can begin.

As a courtesy, automated continuing review reminders can be set-up by PIs at various intervals (75 days, 45 days, 30 days, for example) on the website at https://irb.ucsd.edu. However, as these are automated electronic messages based on data entered, and the HRPP cannot anticipate which type of software programs (such as spam-blockers or anti-virus software) may block receipt of the messages, **PI's are required to not rely upon notification, but have internal mechanisms which track continuing review submission times**. Ultimately, it is the PI's responsibility to initiate a continuing review application, allowing sufficient time for the review and re-approval process to be completed before the current approval expires.

Continuing review is required even if no changes are made, or if the only study activity is participant follow-up, and even if the only study activity is data analysis.

What happens if there is a lapse in IRB approval?

If the IRB has not reviewed and approved a research study by the study expiration date, **all research activities must stop**. This includes the following:

All research-related interventions or interactions with currently enrolled subjects (unless the IRB finds that it is in the best interests of the individual subjects to continue participating in the research interventions or interactions;*) recruitment and informed consent procedures; and continued collection and/or analysis of data/information.

**Exception:* Research-related interventions or interactions with enrolled subjects may continue if the IRB determines that stopping the research would jeopardize the rights or welfare of current subjects. The IRB will decide which subjects should continue receiving the intervention during the lapse in approval. A request for such an exception must be submitted in writing to the attention of the IRB Chair by the Principal Investigator. If any project activity—even activity required for participant safety—occurs or continues after the expiration date, the investigator is out of compliance with both federal regulations and university policy. Retrospective approval for work done after the expiration date cannot be granted.

Amendment/revision to an IRB approved study

IRB approval is required before implementing any changes in the approved research plan, consent documents, recruitment materials, or other study-related documents. Please see Amendment Fact Sheet at http://irb.ucsd.edu/amendmodchg.pdf for submission guidance.

Adverse Event and Unanticipated Problems Reporting

All problems having to do with subject safety must be reported to the IRB within ten working days. All deaths, whether or not they are directly related to study procedures, must be reported. For adverse events, please utilize the form found at https://irb.ucsd.edu/UPR_biomedical.doc. For deviations and other reports, a cover letter and any supplemental information appropriate to the review should be provided. Please see IRB Guidelines for more information at https://irb.ucsd.edu.

Changes in financial Interest or Conflict of Interest (COI) disclosure

Any changes in the financial relationship between the study sponsor and any of the investigators on the study and/or any new potential conflicts of interest must be reported immediately to the Independent Review Committee via the Conflict of Interest Office. If these changes affect the conduct of the study or result in a change in the required wording of the approved consent form, then these changes must also be submitted as an amendment request.