Document Coversheet

Study Title: A Phase I/Ib Study on the Safety of Epidiolex in Patients With Prostate Cancer With Rising PSA After Localized Therapy With Either Surgery or Radiation

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	1/12/2023
NCT Number:	NCT04428203
IRB Number	56982
Coversheet created:	5/2/2023

PROTOCOL TYPE (VERSION 4)

Which IRB

◉ Medical ○ NonMedical

Protocol Process Type

○ Exemption
◉ Expedited (Must be risk level 1)
○ Full

IMPORTANT NOTE: You will not be able to change your selections for "Which IRB" and "Protocol Process Type" after saving this section. If you select the wrong IRB or Protocol Process Type, you may need to create a new application.

See below for guidance on these options, or refer to ORI's "Getting Started" page. Please contact the Office of Research Integrity (ORI) at 859-257-9428 with any questions prior to saving your selections.

Which IRB

The **Medical IRB** reviews research from the Colleges of:

- Dentistry
- Health Sciences
- Medicine
- Nursing
- Pharmacy and Health Sciences
- and Public Health.

The **Nonmedical IRB** reviews research from the Colleges of:

- Agriculture
- Arts and Sciences
- Business and Economics
- Communication and Information
- Design; Education
- Fine Arts
- Law
- and Social Work

Note: Studies that involve administration of drugs, testing safety or effectiveness of medical devices, or invasive medical procedures must be reviewed by the **Medical IRB** regardless of the college from which the application originates.

Which Protocol Process Type

Under federal regulations, the IRB can process an application to conduct research involving human subjects in one of three ways:

- by exemption certification
- by expedited review.
- by full review;

The investigator makes the preliminary determination of the type of review for which a study is eligible. Please refer to ORI's "Getting Started" page for more information about which activities are eligible for each type of review.

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

EXPEDITED CERTIFICATION

0 unresolved comment(s)

To Be Completed Only If Protocol is to Receive Expedited Review

Applicability

A. Research activities that (1) present no more than *minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
B. The categories in this list apply regardless of the age of subjects, except as noted.
C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
D. The expedited review procedure may not be used for classified research involving human subjects.
E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.

**"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests. 45 CFR 46.102(i)*

Check the appropriate categories that apply to your research project:

☑ Study was originally approved by the full IRB at a convened meeting.

☐ 1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

A. Research on drugs for which an investigational new drug application is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
B. Research on medical devices for which (i) an investigational device exemption application is not required*; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.**

* Study must meet one of the IDE Exempt categories listed on the Device Form Attachment.
** An approved Device used in research according to its approved labeling is considered Exempt from IDE requirements.
NOTE: Select Category 1 for compassionate use medical device applications or individual patient expanded access investigational drug applications for which FDA has waived the requirement for full review.

☐ 2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

A. From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
B. From other adults and children* considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

NOTE: Intravenous (IV), Port, Central, or any other lines are NOT eligible under this category even if the research involves "minimal risk".

*In Kentucky, "child/children" refers to all individuals less than 18 years of age unless the individual(s) is/are legally emancipated. (See Informed Consent SOP for discussion of "Emancipated Individuals" under Kentucky state law.) Individuals less than 18 years of age who are not emancipated meet the federal definition for "child" (e.g., DHHS, FDA, and U.S. Department of Education). Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." If conducting research outside the state of Kentucky, you are responsible for complying with applicable state law.

☐ 3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

A. Hair and nail clippings in a nondisfiguring manner;
B. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
C. Permanent teeth if routine patient care indicates a need for extraction;
D. Excreta and external secretions (including sweat);
E. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
F. placenta removed at delivery;
G. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
H. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
I. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
J. Sputum collected after saline mist nebulization.

☐ 4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:

A. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
B. Weighing or testing sensory acuity;
C. Magnetic resonance imaging;
D. electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
E. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

☐ 5) Research involving materials (data, documents, records, or specimens) that have been or will be collected solely for non-research purposes (such as medical treatment or diagnosis) as well as research involving existing information or specimens that were previously collected for research purposes, provided they were not collected for the currently proposed research. (Note: Some research in this category may qualify for Exempt review. This listing refers only to research that is not exempt.)
(Note: If submission includes materials previously collected for either non-research or research purposes in a protocol for which IRB approval expired, you may check Category 5. However, a separate category must also be selected for prospective collection of data/specimens obtained solely for research purposes)

☐ 6) Collection of data from voice, video, digital, or image recordings made for research purposes.

☐ 7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. This listing refers only to research that is not exempt.)

PROJECT INFORMATION

1 unresolved comment(s)

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

MCC-19-GU-74: A phase I/Ib Study on the Safety of Epidiolex in Patients with Prostate Cancer with Rising PSA after Localized Therapy with either Surgery or Radiation

Short Title Description
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

MCC-19-GU-74

Anticipated Ending Date of Research Project: 3/31/2032

Maximum number of human subjects (or records/specimens to be reviewed) 24

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? ○ Yes ◉ No

RISK LEVEL

0 unresolved comment(s)

Indicate which of the categories listed below accurately describes this protocol

- (●) (Risk Level 1) Not greater than minimal risk
- ( ) (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects
- ( ) (Risk Level 3) Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ( ) (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

*****For Expedited and Exempt Applications, the research activities must be Risk Level 1 (no more than minimal risk to human subjects).*****

Refer to UK's guidance document on assessing the research risk for additional information.

SUBJECT DEMOGRAPHICS **0 unresolved comment(s)**

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc..) 18 to 99

Study Population:

Describe the characteristics of the subject population, including age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- Justification for the inclusion of vulnerable groups such as children, prisoners, adults with impaired consent capacity, or others who may be vulnerable to coercion or undue influence.

Please consider these resources:
NIH Diversity Policy
FDA Diversity Guidance

3.1 Inclusion Criteria

3.1.1 Completion of localized therapy (prostatectomy or radiotherapy) for prostate adenocarcinoma (either histologically or cytologically confirmed)

3.1.2 Biochemical (PSA) recurrence, defined as:
- PSA of =0.2 ng/ml that has increased above nadir following radical prostatectomy;
or
- PSA increase of 2.0 ng/ml above post-therapy nadir after primary radiotherapy.
or
- PSA = 0.2 ng/ml after primary radical prostatectomy followed by salvage radiotherapy.

NOTE: PSA measured at two consecutive timepoints (separated by 4 or more weeks) is required in order to demonstrate the requisite increase in PSA

3.1.3 Age =18 years.

3.1.4 ECOG performance status =2 (see Appendix A).

3.1.5 Adequate organ and marrow function at baseline (pre-study) as defined below:
? absolute neutrophil count =1,500/mcL
? platelets =80,000/mcL
? Total Bilirubin: < institutional upper limit of normal
? AST(SGOT)/ALT(SGPT) < institutional upper limit of normal
? glomerular filtration rate (GFR) =30 mL/min/1.73 m2 using the Cockcroft-Gault formula

3.1.6 Patients with a prior or concurrent malignancy (non-prostate) whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen as determined by the treating physician are eligible.

3.1.7 Given that worsening of an underlying state of mental depression or suicidal ideation has been reported with Epidiolex, patients should be carefully screened for depression at baseline and if there are indications or a history of depression it is strongly recommended that these patients be closely followed together with behavioral health or psychiatric medical support. Patients with an established diagnosis of depression that, in the assessment of the investigator may make the administration of Epidiolex hazardous, should not be enrolled on this protocol.

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 History of hypersensitivity to Epidiolex (cannabidiol) or sesame seeds (one of the inactive ingredients in Epidiolex)

3.2.2 Any radiological evidence of metastatic disease (determined by standard of care CT scans of abdomen. pelvis, chest, whole body bone scan or Axium PET/CT scan). Questionable lesions on bone scan will be confirmed by standard of care methods such as plain X-rays or Axium PET/CT scan, if not previously performed.

3.2.3 Receipt of prior cytotoxic chemotherapy for recurrent prostate cancer

3.2.4 Use of androgen deprivation therapy (for example, bicalutamide, flutamide, niluamide, or leuprolide acetate) concurrently or within the previous 3 months.

3.2.5 Uncontrolled intercurrent illness such as active infections. Other illnesses will be evaluated and eligibility status determined at the discretion of the treating physician and the investigator.

3.2.6 Psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Concomitant use of Valproate or Clobazam.

3.2.8 Concurrent use of over-the-counter CBD oil, Marinol or marijuana is not permitted. Patients with a history of current over-the-counter CBD oil, Marinol or marijuana use for any reason are eligible only if they do the following:
- complete a one-week washout period prior to study initiation
- refrain from non-study related CBD oil, Marinol or marijuana use while on-study

3.2.9 Treatment with sensitive substrates of CYP2C19 inhibitors should not be taken within 14 days prior to first dose of study treatment and for the duration of study.

3.3 Inclusion of Women and Minorities

Prostate Cancer occurs exclusively in men, so women are excluded from this study.

Attachments

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: Census Regional Analyst Edition, Kentucky Race/Ethnic Table, Kentucky Population Data.
(Please note: The IRB will expect this information to be reported at Continuation Review time for Pre-2019 FDA-regulated Expedited review and Full review applications):

Participant Demographics

	Cisgender Man	Cisgender Woman	TGNB/TGE	Unknown/Not Reported
American Indian/Alaskan Native:				
Asian:				
Black/African American:	2			
Latinx:				
Native Hawaiian/Pacific Islander:				
White:	18			
American Arab/Middle Eastern/North African:				
Indigenous People Around the World:				
More than One Race:				
Unknown or Not Reported:	1			

If unknown, please explain why:

Indicate the categories of subjects and controls to be included in the study. You may be required to complete additional forms depending on the subject categories which apply to your research. If the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check populations which the research does not specifically target. For example: a large record review of a diverse population may incidentally include a prisoner or an international citizen, but you should not check those categories if the focus of the study has nothing to do with that status.

Check All That Apply (at least one item must be selected)

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal Material
- ☐ Prisoners
- ☐ Non-English Speaking (translated long or short form)

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook for more information on:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults
- Economically or Educationally Disadvantaged Persons

Other Resources:

- UKMC Residents or House Officers [see requirement of GME]

- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

- Non-English Speaking [see also the E-IRB Research Description section on this same topic]
- International Citizens [DoD SOP may apply]
- Military Personnel and/or DoD Civilian Employees

Assessment of the potential recruitment of subjects with impaired consent capacity (or likelihood):

☐ Check this box if your study does NOT involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). If there is no direct intervention/interaction you will not need to answer the impaired consent capacity questions.

Does this study focus on adult subjects with any conditions that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes and you are not filing for exemption certification, go to "Form T", complete the form, and attach it using the button below.

Examples of such conditions include:

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

INFORMED CONSENT/ASSENT PROCESS/WAIVER

1 unresolved comment(s)

For creating your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

Consent/Assent Tips:

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a "Reliance Consent Form" so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".
- It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.
- Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.
  Document Types that do NOT get an IRB approval stamp are:
  - "Highlighted Changes",
  - "Phone Script", and
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

How to Get the Section Check Mark

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a PDF**.
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☐ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☑ Stamped Consent Doc(s) Not Needed

Attachments

Informed Consent Process:

Using active voice, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained

- the timing of the consent process (including any waiting period between providing information and obtaining consent)
- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

The informed consent shall be provided as a standard written statement, written in non-technical language. No patient can enter the study before his informed consent has been obtained. The informed consent form is considered to part of the protocol, and must be submitted by the investigator with the protocol at the time of IRB review.
Requests for information about the research or complaints will be addressed to the PI, research staff, or Office of Research Integrity as appropriate. All requests or complaints will be handled in a timely, courteous, and confidential manner following University policies.

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, complete, Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting a waiver of the requirement for the informed consent process.

☐ I am requesting an alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered and/or omitted, and justify the alteration.

SECTION 2.

Explain how each condition applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

e) If the research involves using or accessing identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

- Private information/specimens are "identifiable" if the investigator may ascertain the identity of the subject or if identifiers are associated with the information (e.g., medical records). This could be any of the 18 HIPAA identifiers including dates of service.
- If not using identifiable private information or identifiable biospecimens, insert N/A below.

Request for Waiver of Signatures

If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (e.g., a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk to the subject, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study.

*If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the **Cover Letter Template** as a guide. There is an English and a Spanish version.*

Option 1

Describe how your study meets these criteria:

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

Option 2

Describe how your study meets these criteria:

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

Option 3

Describe how your study meets these criteria:

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

STUDY PERSONNEL **0 unresolved comment(s)**

Do you have study personnel who will be assisting with the research?
After selecting 'Yes' or 'No' you must click the 'Save Study Personnel Information' button.

◉ Yes ○ No

Manage Study Personnel

Identify other study personnel assisting in research project:

- The individual listed as PI in the 'PI Contact Information' section should NOT be added to this section.
- If the research is required for a University of Kentucky academic program, the faculty advisor is also considered study personnel and should be listed below. ***Residents and students who are PI's are encouraged to designate the faculty advisor or at least one other individual as a contact with an editor role (DP).***
- Role: DP = Editor (individual can view, navigate, and edit the application for any review phase (IR, CR/FR, MR) or 'Other Review", and submit Other Reviews on behalf of the PI.)
- Role: SP = Reader (individual can view and navigate through the currently approved application only.)

To add an individual via the below feature:

- Search for personnel;
- Click "select" by the listing for the person you want to add;
- For each person, specify responsibility in the project, whether authorized to obtain informed consent, AND denote who should receive E-IRB notifications (contact status).

NOTE: Study personnel must complete human subject protection (HSP) and Responsible Conduct of Research (RCR) training before implementing any research procedures. For information about training requirements for study personnel, visit UK's HSP FAQ page, the RCR Getting Started page, or contact ORI at 859-257-9428. If you have documentation of current HSP training other than that acquired through UK CITI, you may submit it to ORI (HSPTrainingSupport@uky.edu) for credit.

Study personnel assisting in research project:

Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	(RCR)	Removed?	Last Updated	SFI
Brooks	Margaret	Study Coordinator	DP	Y	N		P	Y	06/04/2021	Y	N	02/01/2022	N
Childs	Jefferson	Study Coordinator	DP	N	N		P	Y	12/23/2022	Y	N	03/25/2020	N
Chitwood	Holly	Study Coordinator	SP	N	N		P	Y	12/16/2022	Y	N	03/26/2020	N
Comer	Elisha	Data Analysis/Processing	SP	N	N		P	Y	01/03/2022	Y	N	03/18/2020	N
Cornette	Abagail	Study Coordinator	DP	Y	N		P	Y	12/07/2020	Y	N	07/29/2020	N
Duvall	Gary	Study Coordinator	DP	Y	Y		P	Y	05/14/2021	Y	N	02/01/2022	N
England	Shawn	Study Coordinator	DP	N	N		P	Y	02/27/2021	Y	N	03/25/2020	N
Fernand	Anthony	Study Coordinator	DP	N	N		P	Y	05/31/2022	Y	N	03/26/2020	N
Foley	Trent	Study Coordinator	DP	Y	N		P	Y	08/31/2021	Y	N	02/01/2022	N
Hanley	Katherine	Study Coordinator	SP	N	N		P	Y	03/16/2021	Y	N	07/29/2020	N
Hawthorne	Kelly	Study Coordinator	SP	N	N		P	Y	05/05/2021	Y	N	07/29/2020	N
Heath	Heather	Study Coordinator	DP	Y	N		P	Y	08/01/2022	Y	N	07/29/2020	N
Hines	Sarah	Study Coordinator	SP	N	N		P	Y	01/12/2023	Y	N	03/26/2020	N
James	Andrew	Co-Investigator	DP	Y	N	M.D.	P	Y	05/22/2020	Y	N	03/18/2020	N
Kolesar	Jill	Co-Investigator	DP	Y	N	Pharm.	P	Y	09/11/2022	Y	N	03/18/2020	N
Murphy	Sharon	Study Coordinator	DP	N	Y		P	Y	07/22/2022	Y	N	09/06/2022	N
Myers	Adria	Study Coordinator	SP	N	N		P	Y	09/21/2020	Y	N	03/26/2020	N
Napier	Dana	Data Collection	SP	N	N		P	Y	10/28/2021	Y	N	03/18/2020	N
Pavlik	Heather	Study Coordinator	DP	Y	N		P	Y	08/25/2021	Y	N	07/29/2020	N
Penix	Madison	Study Coordinator	DP	N	N		P	Y	08/15/2022	Y	N	09/06/2022	N
Reusch	Ellen	Study Coordinator	DP	Y	N		P	Y	03/03/2020	Y	N	07/29/2020	N
Reynolds	Jeri	Study Coordinator	DP	Y	Y		P	Y	06/03/2022	Y	N	07/29/2020	N
Temple	Stephanie	Study Coordinator	DP	N	N		P	Y	06/04/2021	Y	N	03/25/2020	N
Yeager	Leah	Study Coordinator	SP	N	N		P	Y	09/19/2022	Y	N	03/26/2020	N
Gill	Love	Study Coordinator	DP	N	N		P	Y	10/20/2022	Y	Y	02/01/2022	N
Leedham	Cynthia	Study Coordinator	DP	Y	N		P	Y	10/12/2022	Y	Y	02/01/2022	N
Maloney	Patrick	Study Coordinator	SP	N	N		P	Y	12/21/2021	Y	Y	12/20/2022	N

Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	(RCR)	Removed?	Last Updated	SFI
Momo	Harry	Study Coordinator	DP	Y	N		P	N	10/29/2018	N	Y	02/22/2022	N
Strup	Stephen	Co-Investigator	DP	Y	N	M.D.	P	Y	05/15/2022	Y	Y	03/11/2022	N
Tillman	Kevin	Study Coordinator	DP	Y	N		P	Y	07/06/2020	N	Y	12/20/2022	N
Wang	Peng	Co-Investigator	DP	Y	N	M.D.	P	Y	08/04/2022	Y	Y	12/20/2022	N
Wells	Chad	Study Coordinator	DP	N	Y		P	Y	09/02/2020	Y	Y	12/20/2022	N

RESEARCH DESCRIPTION

0 unresolved comment(s)

You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.

Pro Tips:

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section or under the Additional Information section to include supplemental information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

Biochemically recurrent (BCR) prostate cancer is an increasingly common disease state, with more than 25,000 cases annually [1]. Approximately 30-40% of all prostate cancer patients will develop biochemical or PSA recurrence within 10 years [2]. Whereas, high-risk localized prostate cancer patients (50-90%) have a higher rate of BCR progression [1]. In 2007, the American Urological Association defined biochemical recurrence after radical prostatectomy as an initial PSA level of = 0.2 ng/ml and with a second test confirming levels of > 0.2 ng/ml without radiological or clinical progression [3]. The natural history of PSA recurrence is usually long but can be varied. In a longitudinal cohort of 379 men followed for 22 years, the median time from PSA recurrence to prostate cancer death was not reached after 16 years [4]. In spite of this, prostate cancer deaths are occasionally seen as early as 1 year after PSA recurrence. Thus, although the natural history of recurrent prostate cancer is often one of a slowly progressive disease spanning years or decades, it can also be very rapid in a subset of patients. Moreover, 90% of all recurrences after radical prostatectomy were found within 5 years of prostatectomy as per Duke Prostate Cancer Database [5]. Patients who had early (=¬5 years) PSA recurrence have greater risk for cancer-death compared to those that recur >5 years post radical prostatectomy [5]. It has been shown that rapid prostate specific antigen doubling time (PSADT) is closely linked with risk for prostate cancer death and overall survival [4, 6]. Among men with a PSADT > 3 months after either RP or RT, PSADT as a continuous variable was significantly associated with prostate cancer death [6]. It has become common in clinical practice to make treatment decisions for men with PSA recurrence based on small changes in PSA level, PSADT, Gleason score and time to PSA recurrence [4, 8-10]. The clinical entity of recurrent prostate cancer is fairly common, affecting many current era patients and the subject of many encounters by urologists, radiation oncologists, and medical oncologists.

It is challenging to treat because of the absence of radiographic disease to monitor response. There is no clear consensus on when to begin androgen deprivation therapy (ADT), and the optimal duration of ADT in men with BCR. ASCO updated consensus panel recommendations in 2007, the authors refrained from strongly recommending early ADT initiation [11]. The Veterans Administration Cooperative Urological Research Group found no difference in overall survival when they compared early with deferred hormonal therapy [12]. Moul et al. reviewed data from 1,352 men with postsurgical PSA recurrence and found that, early ADT had no effect on time to metastasis [13]. However, among those with high-risk disease, (pathologic Gleason =8 or PSADT <12 months, early ADT (i.e., starting when the PSA was <5 or < 10 ng/ml) was associated with a 50% reduction in the risk of metastasis after a median follow-up of 3.7 years after PSA recurrence [13]. Unfortunately, follow-up was too short to assess the association between timing of ADT and prostate cancer mortality. Garcia-Albenix et al. analyzed 2,096 men experiencing biochemical recurrence after initial treatment from the CaPSURE registry (Cancer of the Prostate Strategic Urologic Research Endeavour) [14]. The effect of immediate ADT initiation (within 3 months of PSA relapse) on overall survival and prostate-cancer specific survival was evaluated, in comparison to deferred ADT (initiated at the development of metastases, symptoms or a short PSA doubling time). The adjusted mortality hazard ratio for immediate ADT versus deferred ADT was 0.91 (95% CI, 0.52-1.60), demonstrating no significant advantage to early initiation of ADT [14]. ADT confers significant decrements to functioning and quality of life, including sleep disturbance, hot flushes, breast enlargement and tenderness, mood swing, and increased risk of cardiovascular-related death have been observed [15-16]. Thus, the treatment decision for biochemical recurrence is complicated by the need to balance the efficacy of the therapy (gains in overall and disease-specific survival) against minimization of side effects and decline in quality of life in this generally asymptomatic population.

Myriad alternative therapies for BCR have been investigated. Celecoxib treatment for post-RP BCR decreased PSA velocity [17]. Increased intake of vegetable proteins while decreasing animal protein and saturated fat consumption [18] or intake of a soy-based dietary supplement prolonged PSA velocity among men with BCR [19]. NCCN recommends in those population expectant management is also appropriate given the known toxicity of ADT and with the unclear benefit [20]. Thus, ongoing investigation and development of non-hormonal therapies is in demand.

Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

Primary Objective

To determine the Maximum Tolerated Dose of Epidiolex (CBD) in patients with biochemically recurrent prostate cancer

Secondary Objectives

To fully assess the safety and tolerability of CBD in patients with biochemically recurrent prostate cancer.
To measure change in serial PSA and testosterone levels from baseline throughout the treatment period as an indication of biochemical response
To assess health-related quality of life (EORTC QLQ C-30 and PR-25)

Exploratory Objective

Primary tumor from prostatectomy specimen will be assessed for CBD receptor 1 and 2 expression levels, among patients for whom archival surgical specimens are available.

Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.
- *Community-Based Participatory Research*: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

This is a phase I dose escalation study with expansion cohort. Dose escalation will be determined by a Bayesian optimal interval design (BOIN) design [41]. Patients are enrolled in cohorts with 3 patients in each cohort. The primary endpoint is the DLT rate at each dose level. DLT rate is calculated as the total number of patients experienced DLTs at the current dose level divided by the total number and number of patients treated at the current dose level using the DLT. The calculation of DLT rate will only include DLT evaluable patients. The primary endpoints is to find the maximum tolerated dose.
-In the first cohort, a patient is considered evaluable if he completes 75% of doses. Patients that are not evaluable will be replaced.
- In the dose expansion cohort, a patient is considered evaluable if he completes 75% of the planned dosing.

Dose Escalation / De-escalation Decision Rule

Number of patients Treated
Decision Rule 1 2 3 4 5 6 7 8 9
Escalate (or highest) if # DLT >= 0 0 0 0 1 1 1 1 2
De-escalate (or lowest) if # DLT >= 1 1 2 2 2 3 3 3 4
Eliminate (or stop) if # DLT >= -- -- 3 3 4 4 5 5 5

The secondary endpoints include assessment of biochemical response via serial PSA and serial testosterone levels, and health-related quality of life (as assessed by the EORTC QLQ C-30 and PR-25).

The correlative endpoint includes CBD receptor 1 and 2 expression levels.

Sample Size/Accrual Rate

We plan to enroll up to 9 DLT evaluable patients for dose escalation to establish the MTD.

Once we have established the MTD, we will begin treating 6 to 9 more patients at the MTD level in an expansion cohort to confirm safety and explore evidence of efficacy of the study treatment. The number of patients to be enrolled in expansion cohort depends on the number of non-DLT evaluable patients in the dose escalation part of the study. If all patients in the dose escalation part of the study are DLT evaluable, we will have enroll 9 more patients, otherwise, we will subtract the number of non-DLT evaluable patients from expansion cohort. The total sample size for this study is 18 (enrolled) patients with about 12 patients treated at the MTD.

Analysis of Primary Endpoint

The dose escalation and MTD will be determined by the posterior distribution of Pr(DLT) estimate [41]. The target toxicity probability is set at 30%. Safety and tolerability of Epidiolex will be monitored and assessed. AE counts will be summarized by descriptive statistics.

Analysis of Secondary Endpoints

Change of PSA and testosterone levels from baseline throughout the 90-day treatment period will be represented by longitudinal

profiles and analyzed by mixed effects model. Baseline is defined as the last non-missing PSA measurement prior to administrating study drug. PSA and testosterone levels may be categorized and summarized by response rates with confidence intervals.

The Quality of Life scores collected longitudinally will be analyzed using appropriate linear models for repeated measures data.

Analysis of Correlative Endpoints

Post-hoc analyses will be conducted on correlative endpoints with appropriate statistical methods depending on distribution and availability of collected data.

Attachments

Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

Subjects will be identified by referral from community oncologists and primary care physicians, as well as internal referrals from physicians at the University of Kentucky. Subjects will initially be evaluated by treating oncologist, and will be offered initial information about the clinical trial if appropriate. Agreeable subjects will then be invited to participate in an informed consent process as described in this research description. The study will be posted on the website of the Markey Cancer Center in the general
No advertising without prior IRB approval will be used, except for recruitment plans described previously; however, the sponsor may issue press releases to the media without our knowledge.

Attachments

Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

Pre study screening
• Quality of Life survey
• Informed consent discussed and signed
• Demographic information given
• One blood draw for PSA test and total testosterone as a standard part of treatment
• Imaging scans done and the results assessed to see if the cancer has gotten worse.
o PET or PET/CT scan at the PI's discretion
o Bone scan at the PI's discretion
o CT chest, abdomen, pelvis scans at the PI's discretion
o MRI of the pelvis
• Urine THC screening test
• EKG a test that measures the heartbeat.
• CBC: A routine blood test used to measure the ratios of different blood cell counts to see if any are out of alignment
• CMP: A routine blood test used to examine overall metabolism and identify any potential problems
• Venipuncture for the blood tests described above
• Concomitant Medications where the doctor will assess any current medications to make sure nothing will have side effects with the Epidiolex.
• Medical History
• Height determined
• Physical exams with vitals determined and ECOG performance evaluation
• ECOG performance evaluation
• Archival tissue collection

Day 1 Expidiolex administration
• Administration of epidiolex
• Assessment of the disease progression
• CBC: A routine blood test used to measure the ratios of different blood cell counts to see if any are out of alignment
• CMP: A routine blood test used to examine overall metabolism and identify any potential problems
• Possible Physical exam if your doctor determines it is needed
• ECOG performance evaluation at the discretion of the PI.

Day 30-60-90 Expidiolex administrations
• Administration of epidiolex
• Evaluation of any symptoms known as adverse events
• Evaluating dose level based on symptoms
• Making sure you are following instructions
• One blood draw for PSA test and total testosterone as a standard part of treatment
• All the above scans can be repeated per NCCN guidelines or more often as clinically indicated by suspected disease progression.
o PET or PET/CT scan at the PI's discretion
o Bone scan at the PI's discretion
o CT chest, abdomen, pelvis scans at the PI's discretion
o MRI of the pelvis
• Assessment of the disease progression
• EKG a test that measures the heartbeat.
• CBC: A routine blood test used to measure the ratios of different blood cell counts to see if any are out of alignment
• CMP: A routine blood test used to examine overall metabolism and identify any potential problems
• Venipuncture for the blood tests described above
• Concomitant Medications where the doctor will assess any current medications to make sure nothing will have side effects with the Epidiolex.
• Physical exams with vitals determined and ECOG performance evaluation

30 days after treatment
• Evaluation of any symptoms known as adverse events
• One blood draw for PSA test and total testosterone as a standard part of treatment

• All the above scans can be repeated per NCCN guidelines or more often as clinically indicated by suspected disease progression.
o PET or PET/CT scan at the PI's discretion
o Bone scan at the PI's discretion
o CT chest, abdomen, pelvis scans at the PI's discretion
o MRI of the pelvis
• CBC: A routine blood test used to measure the ratios of different blood cell counts to see if any are out of alignment as determined by the PI
• CMP: A routine blood test used to examine overall metabolism and identify any potential problems as determined by the PI
• Physical exams with vitals determined and ECOG performance evaluation as determined by the PI.

Attachments

Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

DLT rate at each dose level
Assessment of biochemical response via serial PSA
Serial testosterone levels
Quality of Life assessment

Attachments

Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

Research staff of the Markey Cancer Center Clinical Research Organization with oncology research related experience, ranging from one to thirteen years, will assist the PI in the conduct of the study. All subjects will have study medication dispensed in the Markey Cancer Center's closely monitored clinic area, with on-site pharmacy and medical support, certified oncology nurses and ready access to emergency care. The University's social services, patient advocate, and Office of Research Integrity are readily available to provide support or services as needed. This study utilizes additional Key Personnel identified on the protocol "15-MCCCRO-KP:MCC-CRO Master SP List."

Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

In 100 people receiving Epidiolex, more than 10 and up to 100 may have:
• Decreased appetite
• Diarrhea
• Transaminase elevations (changes in your bloodwork that can signify liver damage)
• Fatigue
• Malaise (feeling uncomfortable, ill or lack of energy but you cannot explain the cause)
• Asthenia (physical weakness or lack of energy)
• Rash
• Infection
• Insomnia
·Somnolence (sleepiness or drowsiness)

Allergic Reactions
As with any drug, it is possible that patients could have allergic reactions to study drug, such as itching, skin rash, facial swelling, and/or a severe or sudden drop in blood pressure. A sudden drop in blood pressure could lead to loss of consciousness and/or possible seizures and could progress to the possibility of significant side effects including death.

Blood Sampling
Having blood drawn from a vein may cause some pain, soreness, possible fainting, bleeding, redness, or bruising where the needle is inserted. An infection is also possible, but rare.

Electrocardiogram (ECG)
A patient's skin may react to the sticky patches that attach the detectors (electrodes) to the chest for the ECG. This skin irritation usually disappears when the patches are removed

Reproductive Risks
Subjects should not father a baby while on this study because Epidiolex may involve risks to the embryo or fetus. Patients will be instructed to tell the study doctor if their partner become pregnant anytime during the study or within 3 months of stopping the study drug.
Patents have the potential to experience an improvement on their health via treatment

Available Alternative Opportunities/Treatments

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

Subjects who do not want to take part in the study have other choices such as:
• Getting treatment or care for your cancer without being in a study. Standard of care for this type of cancer may include observation or radiation therapy or hormonal therapy;
• Taking part in another study of an investigational drug;
• Getting no treatment.

Back to Top

Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies
FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy

Digital Data

Specimens from subjects (either archival or fresh tumor tissue) are reviewed to confirm diagnosis for participation in the study. Medical/Clinical information pertaining to protocol is included in the subjects' medical records. Copies are also kept in subjects' protocol chart. This ensures timely record review, and allows for collection of data points required to meet primary and secondary objectives of the study.
Confidentiality of medical information is discussed at length in the informed consent. Subjects are made aware of what data will be collected, where it is stored and who has access to the information. Study data may be published or shared with other researchers, but the identity and medical history of each study participant will remain strictly confidential. Representatives of University of Kentucky, the Food and Drug Administration (FDA), the National Cancer Institute (NCI), or representatives and the Institutional Review Board (IRB) may view study data and information.

During the study, information will be collected to assess compliance with the study requirements. These records will be used by the FDA, the IRB, and the Investigator(s) in connection with complying with their obligations relating to this study. The records will not be used for any other purposes or disclosed to any other party without the subject's permission. All records will be coded with an identification number to protect their identity. Data will be stored in a secured area for at least two years after the study is completed. All data stored is on site at Markey Cancer Center Clinical Research Organization in locked facilities, and with limited access to records by designated research staff. All research records will be held for a minimum of six years following completion of the study
Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety assessments will consist of monitoring and recording of all Adverse Events (AEs) and all serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s). Patients will be evaluated for all adverse events for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated approximately 30 days (between 30 and 37 days) after the decision to discontinue treatment.

Safety will be evaluated from the incidence of all AEs including SAEs and the severity of AEs according to the NCI CTC guidelines. Reporting guidelines for AEs will comply with the University of Kentucky's IRB requirements and are extensively described in the clinical protocol. To minimize risks, tests are performed at intervals to monitor the clinical status of the subject. Confidentiality of medical information is discussed at length in the informed consent. Subjects are made aware of what data will be collected, where it is stored and who has access to the information. To assure necessary medical intervention in the event of an adverse experience, patients are asked to notify their physician in the event of any adverse experience in the consent. The patients are interviewed at each clinic visit by the research staff and are specifically asked if they have had any adverse experiences. Adverse events from ongoing studies are reviewed as the sponsor submits them to the PI and if necessary patients are contacted concerning any new information; and the information is added to the "Risks and/or Discomforts" section of the consent form as determined by the PI and/or Sponsor

UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Do you confirm that you will retain all IRB-related records for a minimum of 6 years after study closure?

◉ Yes ○ No

Back to Top

Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered, indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

Subjects will not receive any rewards or payment for taking part in this study.

Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is "standard" – and thus not covered by the sponsor/study – unless you tell them.

Subjects will be responsible for the cost of all care and treatment that would normally be done for this condition. The study drug and tests done strictly for research will be paid for by the Sponsor, which include:

Therefore, these costs will be paid for by Markey Cancer Center, the sponsor of this study:
• The costs associated with providing the study drug (Epidiolex)
• Biomarker correlative tests analysis

Data and Safety Monitoring

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

The Principal Investigator has primary responsibility for monitoring the safe conduct of this study. Additionally, the Markey Cancer Center Data Safety and Monitoring Plan outlines oversight and monitoring of all cancer clinical trials. The Committee is responsible for reviewing data to identify patient safety and protocol compliance issues. The Markey Protocol Review Committee (PRC) assigns studies a DSMC review timeline based on the phase, origination of the study and known safety issues.

The members of the MCC DSMC consist of Medical Oncologists, a Pharmacist, a Nurse Manager, a Certified Clinical Research Professional and a Reporter. These members were selected based on their experience, reputation for objectivity, and knowledge of clinical trial methodology. At each meeting, the following data is reviewed by the MCC DSMC: treatment issues, serious adverse events (SAEs) per FDA definitions, dose levels, dose modifications, and responses as applicable.
The DSMC reviews the protocol to assure the following: progress of the trial and safety of participants; compliance with requirements for the reporting of adverse events; any actions resulting in a temporary or permanent suspension by the sponsor; and data accuracy and protocol compliance.

The DSMC, the Protocol Review Committee (PRC), the responsible disease-specific Clinical Care and Research Team (CCART) and/or the UK IRB are empowered to immediately suspend accrual to any study under its purview for any of the following: Failure to comply with AE/SAE reporting requirements; poor study enrollment; protocol violations or issues related to patient safety.

Future Use and Sharing of Research Data

If the results of this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

Your information or samples collected for this study will NOT be used or shared for future research studies, even if we remove the identifiable information like your name, medical record number, or date of birth.

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Recruitment and Consent:

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.
When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

Cultural and Language Consultants:

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.
- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

Local Requirements:

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the “Additional Information/Materials” section. You may also consult the current edition of the International Compilation of Human Research Standards

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?
○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:
Back to Top

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?

○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the investigator assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe the experience/knowledge/training (if any) of the investigator serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if any sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?
○ Yes ○ No

If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

Attachments

HIPAA

0 unresolved comment(s)

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

If yes, check below all that apply and attach the applicable document(s):

- ☐ HIPAA De-identification Certification Form
- ☐ HIPAA Waiver of Authorization

Attachments

STUDY DRUG INFORMATION

0 unresolved comment(s)

The term drug may include:

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?

◉ Yes ○ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Epidiolex

Note: Inpatient studies are required by Hospital Policy to utilize Investigational Drug Service (IDS) pharmacies (Oncology or Non-Oncology). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☑ Investigational Drug Service (IDS) UK Hospital

Other Location:

Is the study being conducted under a valid Investigational New Drug (IND) application?

○ Yes ◉ No

If Yes, list IND #(s) and complete the following:

IND Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Checkmark if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Expanded Access SOP.

Complete and attach the required Study Drug Form picking "Study Drug Form" for the document type. Any applicable drug documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.) should be attached using "Other Drug Documentation" for the document type.

Attachments

Attach Type	File Name
Study Drug Form	ori-f10900-form-o-investigational-drugs-pdf.pdf

STUDY DEVICE INFORMATION

0 unresolved comment(s)

A DEVICE may be a:

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?

○ Yes ◉ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer “no” above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

Is the study being conducted under a valid Investigational Device Exemption (IDE), Humanitarian Device Exemption (HDE) or Compassionate Use?

○ Yes ○ No

If Yes, complete the following:
IDE or HDE #(s)

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment IDE or Compassionate Use under the Food and Drug Administration (FDA) Expanded Access program.

For Individual or Small Group Expanded Access, see FDA's Early Expanded Access Program Information, and attach the following:

- FDA expanded access approval or sponsor’s authorization;
- An independent assessment from an uninvolved physician, if available;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Medical Device SOP.

Does the intended use of any research device being tested (not clinically observed) in this study meet the regulatory definition of Significant Risk (SR) device?

- Yes. Device(s) as used in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- No. All devices, as used in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

Complete and attach the required Study Device Form, picking the "Study Device Form" for the document type. Any applicable device documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.) should be attached using "Other Device Documentation" for the document type.

Attachments

RESEARCH SITES

0 unresolved comment(s)

To complete this section, ensure the responses are accurate then click "SAVE".

A) Check all the applicable sites listed below at which the research will be conducted. If none apply, you do not need to check any boxes.

UK Sites

- ☐ UK Classroom(s)/Lab(s)
- ☑ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☐ UK Healthcare Good Samaritan Hospital
- ☑ UK Hospital

Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

***Fayette Co. School systems, as well as other non-UK sites, have additional requirements that must be addressed. See ORI's IRB Application Instructions - Off-site Research web page for details.**

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Norton Healthcare
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Veterans Affairs Medical Center
- ☐ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☐ International Sites

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky, at sites that are geographically separate from UK, or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page), including:

- A letter of support and local context is required from non-UK sites. See *Letters of Support and Local Context* on the IRB Application Instructions - Off-Site Research web page for more information.
- Supportive documentation, including letters of support, can be attached below.
- NOTE: If the non-UK sites or non-UK personnel are engaged in the research, there are additional federal and university requirements which need to be completed for their participation. For instance, the other site(s) may need to complete their own IRB review, or a cooperative review arrangement may need to be established with non-UK

sites.
- Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

List all other non-UK owned/operated locations where the research will be conducted:

Describe the role of any non-UK site(s) or non-UK personnel who will be participating in your research.

Attachments

B) Is this a multi-site study for which **you are the lead investigator or UK is the lead site**? ○ Yes ◉ No

If YES, describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of protocol modifications and interim results from the non-UK sites:

C) If your research involves collaboration with any sites and/or personnel outside the University of Kentucky, then it is considered multisite research and IRB reliance issues will need to be addressed. This may include national multi-center trials as well local studies involving sites/personnel external to UK. If you would like to request that the University of Kentucky IRB (UK IRB) serve as the lead IRB for your study, or if you would like the UK IRB to defer review to another IRB, please contact the IRBReliance@uky.edu.

RESEARCH ATTRIBUTES

0 unresolved comment(s)

Indicate the items below that apply to your research. Depending on the items applicable to your research, you may be required to complete additional forms or meet additional requirements. Contact the ORI (859-257-9428) if you have questions about additional requirements.

☐ Not applicable

Check All That Apply

	For additional requirements and information:
☐ Academic Degree/Required Research	• Cancer Research (MCC PRMC) • Certificate of Confidentiality (look up "Confidentiality/Privacy...") • CCTS (Center for Clinical and Translational Science)
☐ Alcohol/Drug/Substance Abuse Research	• Clinical Research (look up "What is the definition of....)
☐ Biological Specimen Bank Creation (for sharing)	• Clinical Trial
☑ Cancer Research	• Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection...")
☐ CCTS-Center for Clinical & Translational Science	• Collection of Biological Specimens (look up "Specimen/Tissue Collection...")
☐ Certificate of Confidentiality	• Community-Based Participatory Research (look up "Community-Engaged...")
☑ Clinical Research	• Data & Safety Monitoring Board (DSMB) *For Medical IRB: Service Request Form for CCTS DSMB
☐ Clinical Trial - Phase 1	
☑ Clinical Trial	
☐ Collection of Biological Specimens for internal banking and use (not sharing)	
☐ Community-Based Participatory Research	
☐ Deception	• Data & Safety Monitoring Plan • Deception* *For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Educational/Student Records (e.g., GPA, test scores)	
☐ Emergency Use (Single Patient)	• Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF) • Genetic Research (look up "Specimen/Tissue Collection...") • Gene Transfer • HIV/AIDS Research (look up "Reportable Diseases/Conditions") • Screening for Reportable Diseases [E2.0000] (PDF) • International Research (look up "International & Non-English Speaking") • NIH Genomic Data Sharing (GDS) Policy (PDF) • Planned Emergency Research Involving Waiver of Informed Consent* *For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process" • Use, storage and disposal of radioactive material and radiation producing devices
☐ Gene Transfer	
☐ Genetic Research	
☐ GWAS (Genome-Wide Association Study) or NIH Genomic Data Sharing (GDS)	
☐ Human Cells, Tissues, and Cellular and Tissue Based Products	
☐ Individual Expanded Access or Compassionate Use	
☐ International Research	
☐ Planned Emergency Research Involving Exception from Informed Consent	
☐ Recombinant DNA	
☐ Registry or data repository creation	
☐ Stem Cell Research	
☐ Suicide Ideation or Behavior Research	
☐ Survey Research	
☐ Transplants	
☐ Use, storage and disposal of radioactive material and radiation producing devices	
☐ Vaccine Trials	

FUNDING/SUPPORT

0 unresolved comment(s)

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☐ Not applicable

Check All That Apply

- ☐ Grant application pending
- ☐ (HHS) Dept. of Health & Human Services
  - ☐ (NIH) National Institutes of Health
  - ☐ (CDC) Centers for Disease Control & Prevention
  - ☐ (HRSA) Health Resources and Services Administration
  - ☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
- ☐ (DoJ) Department of Justice or Bureau of Prisons
- ☐ (DoE) Department of Energy
- ☐ (EPA) Environmental Protection Agency
- ☐ Federal Agencies Other Than Those Listed Here
- ☐ Industry (Other than Pharmaceutical Companies)
- ☐ Internal Grant Program w/ proposal
- ☑ Internal Grant Program w/o proposal
- ☐ National Science Foundation
- ☐ Other Institutions of Higher Education
- ☐ Pharmaceutical Company
- ☐ Private Foundation/Association
- ☐ U.S. Department of Education
- ☐ State

Other:

Click applicable listing(s) for additional requirements and information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education
- (DoJ) Department of Justice or Bureau of Prisons
- (DoE) Department of Energy Summary and Department of Energy Identifiable Information Compliance Checklist
- (EPA) Environmental Protection Agency

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

Markey Cancer Center

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application using the "Add Related Grants" button.
If required by your funding agency, upload your grant using the "Grant/Contract Attachments" button.

Add Related Grants

Grant/Contract Attachments

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources. (See DoD SOP and DoD Summary for details)

○ Yes ◉ No

Using the “attachments” button (below), attach applicable materials addressing the specific processes described in the DoD SOP.

DOD SOP Attachments

Additional Certification: (If your project is federally funded, your funding agency may request an Assurance/ Certification/Declaration of Exemption form.) Check the following if needed:

☐ Protection of Human Subjects Assurance/Certification/Declaration of Exemption (Formerly Optional Form – 310)

Assurance/Certification Attachments

OTHER REVIEW COMMITTEES

0 unresolved comment(s)

If you check any of the below committees, additional materials may be required with your application submission.

Does your research fall under the purview of any of the other review committees listed below? [*If yes, check all that apply and attach applicable materials using the attachment button at the bottom of your screen.*]

◉ Yes ○ No

☐ Institutional Biosafety Committee
☐ Radiation Safety Committee
☐ Radioactive Drug Research Committee
☑ Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)
☐ Graduate Medical Education Committee (GME)
☐ Office of Medical Education (OME)

Additional Information

- Institutional Biosafety Committee (IBC) - Attach required IBC materials
- Radiation Safety Committee (RSC) - For applicability, see instructions and attach form
- Radioactive Drug Research Committee (RDRC)
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)** - Attach MCC PRMC materials, if any, per instructions.
- Office of Medical Education (OME)
- Graduate Medical Education Committee (GME)

Attachments

**** If your study involves cancer research, be sure to select "Cancer Research" in the "Research Attributes" section.** ORI will send your research protocol to the Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC). The MCC PRMC is responsible for determining whether the study meets the National Cancer Institute (NCI) definition of a clinical trial and for issuing documentation to you (the investigator) which confirms either that PRMC approval has been obtained or that PRMC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

SUBMISSION INFORMATION

0 unresolved comment(s)

***** If this Continuation Review entails a change in the scope of your activities to include COVID-19 related research, please insert "COVID19" at the start of your Project and Short Titles.*****

Each Section/Subsection in the menu on the left must have a checkmark beside it (except this Submission section) indicating the Section/Subsection has been completed. Otherwise your submission for IRB review and approval cannot be sent to the Office of Research Integrity/IRB.

If applicable, remember to update the Approval Letter Details text box under the Additional Information section

If your materials require review at a convened IRB meeting which you will be asked to attend, it will be scheduled on the next available agenda and you will receive a message to notify you of the date.

If you are making a change to an attachment, you need to delete the attachment, upload a highlighted version that contains the changes (use Document Type of "Highlighted Changes"), and a version that contains the changes without any highlights (use the appropriate Document Type for the item(s)). Do **not** delete approved attachments that are still in use.

Principal Investigator's Assurance Statement

I understand the University of Kentucky's policies concerning research involving human subjects, and I attest to:

1. Having reviewed all the investigational data from this study, including a compilation of all internal and external unanticipated problems.
2. Having reviewed, if applicable, information from the sponsor including updated investigator brochures and data and safety monitoring board reports.

I also attest that I have reviewed pertinent materials concerning the research and concluded either:

A. The human subject risk/benefit relationship is NOT altered, and that it is not necessary to modify the protocol or the informed consent process,
OR,
B. The human subject risk/benefit relationship has been altered, and have previously submitted or am including with this continuation review submission, a modification of the research protocol and informed consent process.

☑ By checking this box, I am providing assurances for the applicable items listed above.

Your protocol has been submitted.

KEY INFORMATION FOR MCC-19-GU-74-PMC: A phase I/Ib Study on the Safety of Epidiolex in Patients with Prostate Cancer with Rising PSA after Localized Therapy with either Surgery or Radiation

We are asking you to choose whether or not to volunteer for a research study about the long-term safety and tolerability of Epidiolex in patients with biochemically recurrent prostate cancer. Biochemical recurrence is a condition where PSA levels rise after treatment for prostate cancer.

You are being asked to take part in this study because you have previously completed localized therapy (prostatectomy or radiotherapy) for prostate adenocarcinoma and your PSA level has risen. This page is to give you key information to help you decide whether to participate. We have included detailed information after this page. Ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is below.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By doing this study, we hope to learn about the short-term side effects as well as the long-term safety and tolerability of different Epidiolex (CBD) doses in patients with biochemically recurrent prostate cancer. We also want to see whether taking Epidiolex (CBD) results in changes to your PSA and testosterone levels. Epidiolex is a CBD oil product FDA approved for the treatment of seizures associated with two rare and severe forms of epilepsy. Epidiolex is not approved for the treatment of prostate cancer but previous studies have shown that it may lower PSA levels. Your participation in this research will last about 120 days.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

Taking part in this study may or may not make your health better. The information from this study will help doctors learn more about using Epidiolex for treatment in prostate cancer and could lead to better treatments in the future. Previous studies suggest that Epidiolex may lower your PSA and/or testosterone levels. For a complete description of benefits, refer to the Detailed Consent.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

You may not want to take part in this study if you are unwilling to stop using non-study related CBD oil, Marinol or marijuana use while on-study. If you are currently using these products, you will have to stop them for a week before going on study. If you are currently depressed or if you have a history of depression, you should discuss this with the study doctor as Epidiolex may worsen these symptoms. You should not take part in this study if you have a history of hypersensitivity to CBD products. You may not want to participate in this study because of the side effects listed in the detailed consent below. For a complete description of risks, refer to the Detailed Consent.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study contact Zin Myint, M.D of the University of Kentucky, Department of Internal Medicine at 859-323-3964 or by mail at University of Kentucky Markey Cancer Center, 800 Rose Street, Lexington, KY 40536

If you have any concerns or questions about your rights as a volunteer in this research, contact staff in the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428.

DETAILED CONSENT:

ARE THERE REASONS WHY YOU WOULD NOT QUALIFY FOR THIS STUDY?
You would not qualify to participate in this study if you are:

• Under the age of 18
•You are currently taking any other investigational agents
•You are unwilling/unable to discontinue use of CBD oil products, Marinol or marijuana
• There are other criteria that must be met to take part in this study that your study doctor will review with you.

WHERE WILL THE STUDY TAKE PLACE AND WHAT IS THE TOTAL AMOUNT OF TIME INVOLVED?

The research procedures will be conducted at University of Kentucky Medical Center and Markey Cancer Center facilities. You will need to come six times during the study. Each of those visits will take about 3 hours. If your disease worsens while you are on the study, you will stop study treatment. If this happens, you will be asked to come in for a final off-study visit that will take about an hour. The total amount of time you will be asked to volunteer for this study is 18 hours over the next 120 days.

WHAT WILL YOU BE ASKED TO DO?

You will be asked if you are interested in taking part in this research study. If you are interested, you will be asked to read this informed consent form and ask any questions you may have and decide whether you want to take part in the study. If you agree to be in the study, you will be asked to sign and date the last page of this form. You will be asked to come in six times for this study. First, you will be asked to come in once for pre-study screening visit to determine if you can join the study, four times for Epidiolex administration, and finally once for follow up after treatment is complete. If your disease progresses (worsens), you will be asked to come in for a final "off-study" visit. See below for detailed list of what will occur at each visit:

Pre-Study Visit (Screening)

- The study doctor will ask you about your medical history, including any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken in the last 90 days or are taking now. Demographic information will also be collected.
- You will have a full physical examination performed by a medical doctor to check your health status. Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured. The study doctor will assess the state of your cancer and how the disease affects your daily living. The doctor will also ask you about any thoughts you may have about death or harming yourself.
- You will be asked to complete two questionnaires about your health.
- You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) for routine tests to evaluate your overall health, organ function as well as your PSA and total testosterone levels.
- You will be asked to provide a urine sample. It will be screened for the presence of THC, which is the compound in cannabis that is psychoactive.
- Electrocardiogram (abbreviated as EKG or ECG) is a test that measures the electrical activity of your heartbeat.
- If you have previous had a biopsy, your archival tumor will be tested to learn more about the Cannabidiol (CBD) levels present in that tissue.
- The scans (PET, CT, MRI, etc.) that you received as part of your standard care will also be used to determine whether you are eligible to be in this study.

All lab tests and scans should be completed within 4 weeks of starting treatment and radiographic studies should be completed within 12 weeks prior to registration/initiation of treatment.

Treatment

Day 1 of taking Epidiolex

If you are eligible to take part in this study, you will be asked to come in for the following procedures.

- You will take Epidiolex by mouth, once a day, on empty stomach on an outpatient basis using the dose assigned to you by the study doctor. You will be asked to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.
- Once you have started the study, the status of your cancer will be assessed using standard scans. If your PSA rises or you experience other clinical systems, the study doctor may ask you to have scans to determine if your cancer is progressing (worsening).
- You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) for routine tests to evaluate your overall health and organ function.
- If necessary, you will have a full physical examination to check your health status, assess the state of your cancer and to determine how your disease affects your daily living.

Day 30, Day 60 and Day 90 after you begin taking Epidiolex

You will be asked to come in for a visit 30, 60 and 90 days after you begin taking Epidiolex.

- You will take Epidiolex by mouth, once a day, on empty stomach on an outpatient basis using the dose assigned to you by the study doctor. You will be asked to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.
- The study doctor will ask you about any side effects you have experienced since the previous visit.
- The study doctor will ask you about your medical history, including any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken in the last 90 days or are taking now.
- You will have a full physical examination to check your health status. Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured. The study doctor will assess the state of your cancer and how the disease affects your daily living. The doctor will also ask you about any thoughts you may have about death or harming yourself.
- You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) for routine tests to evaluate your overall health, organ function as well as your PSA and total testosterone levels.
- Electrocardiogram (abbreviated as EKG or ECG) is a test that measures the electrical activity of the heartbeat.
- During the study, the status of your cancer will be assessed using standard scans. If your PSA rises or you experience other clinical systems, the study doctor may ask you to have scans to determine if your cancer is progressing (worsening).
- You will be asked to complete two questionnaires about your health (Day 90 visit only).

30 days after your last dose of Epidiolex

- The study doctor will ask you about any side effects you have experienced.
- You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) to evaluate your PSA and total testosterone levels. If your doctor thinks it is necessary, she may perform routine tests on your sample to evaluate your overall health and organ function.
- During the study, the status of your cancer will be assessed using standard scans. If your PSA rises or you experience other clinical systems, the study doctor may ask you to have scans to determine if your cancer is progressing (worsening).
- If you doctor feels it necessary, you will have a full physical examination to check your health status. Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured. The study doctor will assess the

state of your cancer and how the disease affects your daily living. The doctor will also ask you about any thoughts you may have about death or harming yourself.

If you begin Androgen deprivation therapy (ADT) at any time during this study, you will be taken off study treatment.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

These side effects are very common but not everyone will necessarily experience them

- Decreased appetite
- Diarrhea
- Transaminase elevations (changes in your bloodwork that can signify liver damage)
- Fatigue
- Malaise (feeling uncomfortable, ill or lack of energy but you cannot explain the cause)
- Asthenia (physical weakness or lack of energy)
- Rash
- Infection
- Insomnia
- Somnolence (sleepiness or drowsiness)
- Mood changes including depressive symptomatology and sometimes suicidal ideation

Allergic Reactions

As with any drug, it is possible that you could have allergic reactions to study drug, such as itching, skin rash, facial swelling, and/or a severe or sudden drop in blood pressure. A sudden drop in blood pressure could lead to loss of consciousness and/or possible seizures and could progress to the possibility of significant side effects including death. If you have any of the above symptoms, seek medical attention right away.

Blood Sampling

Having blood drawn from a vein in your body may cause some pain, soreness, possible fainting, bleeding, redness, or bruising where the needle is inserted. An infection is also possible, but rare. If you feel faint while having your blood drawn, you should sit or lie down to avoid falling.

Electrocardiogram (ECG)

Your skin may react to the sticky patches that attach the detectors (electrodes) to the chest for the ECG. This skin irritation usually disappears when the patches are removed

Reproductive Risks
You should not father a baby while on this study because Epidiolex may involve risks to the embryo or fetus. If your partner becomes pregnant anytime during the study or within 3 months after stopping the study drug, you must immediately tell your study doctor.

Other Risks
There is always a chance that any medical intervention can harm you. In addition to the risks listed above, you may experience a previously unknown risk or side effect.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

There is no guarantee that you will get any benefit from taking part in this study. Your willingness to take part, however, may, in the future, help doctors better understand and/or treat others who have your condition.

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to take part in the study, there are other choices such as:

- Getting treatment or care for your cancer without being in a study. Standard of care at the University of Kentucky for your cancer may include observation or intermittent hormonal therapy;
- Taking part in another study of an investigational drug;
- Getting no treatment.

WHAT WILL IT COST YOU TO PARTICIPATE?

You and/or your insurance company, Medicare, or Medicaid will be responsible for the costs of all care and treatment that you would normally receive for any conditions you may have. These are costs that are considered medically necessary and will be part of the care you receive even if you do not take part in this study.

The University of Kentucky may not be allowed to bill your insurance company, Medicare, or Medicaid for the medical procedures done strictly for research.

Therefore, these costs will be paid for by Markey Cancer Center, the sponsor of this study:

- The costs associated with providing the study drug (Epidiolex)
- Biomarker correlative tests analysis

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

When we write about or share the results from the study, we will write about the combined information. We will keep your name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. At the University of Kentucky, data is stored at the Markey Cancer Center in locked facilities, and with limited access to records by designated research staff. The study doctor will assign you a unique code consisting of a series of numbers and only your unique code, and nothing that could identify you personally, will be entered into the study report forms.

You should know that in some cases we may have to show your information to other people because of state or federal law.

For example, the law may require us to share your information with:

- a court or agencies, if you have a reportable disease/condition;
- authorities, if you report information about a child being abused; or if you pose a danger to yourself or someone else.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- The University of Kentucky Institutional Review Board
- Representatives of the U.S. Food and Drug Administration as required by law
- Representatives of the National Cancer Institute (NCI)
- Representatives of the Kentucky Cancer Registry
- Authorized representatives of the University of Kentucky, UK Hospital, and the Markey Cancer Center

CAN YOU CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can choose to leave the study at any time. You will not be treated differently if you decide to stop taking part in the study.

If you withdraw or are withdrawn, the study drug will no longer be provided free of charge and may not be available commercially.

If you choose to leave the study early, data collected until that point will remain in the study database and may not be removed.

The investigators conducting the study may need to remove you from the study. You may be removed from the study if:

- you are not able to follow the directions,
- we find that your participation in the study is more risk than benefit to you, or
- the agency paying for the study chooses to stop the study early for a number of scientific reasons.

ARE YOU PARTICIPATING, OR CAN YOU PARTICIPATE, IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may not take part in this study if you are currently involved in another research study. It is important to let the investigator/your doctor know if you are in another research study. You should discuss this with the investigator/your doctor before you agree to participate in another research study while you are in this study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that is due to the study, you should call Zin Myint, M.D. at 859-323-3964 immediately. If you should have an emergency after 5pm during the week or on the weekend, please contact UK Paging Operator at (859) 323-5321 and ask to page Dr. Zin Myint and she will determine what type of treatment, if any, is best for you at that time.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study.

Medical costs related to your care and treatment because of study-related harm will be your responsibility;

You do not give up your legal rights by signing this form.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

You will not receive any rewards or payment for taking part in the study.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

We will tell you if we learn new information that could change your mind about staying in the study. We may ask you to sign a new consent form if the information is provided to you after you have joined the study.

WILL YOU BE GIVEN INDIVIDUAL RESULTS FROM THE RESEARCH TESTS?

Generally, tests done for research purposes are not meant to provide clinical information. We will not provide you with individual research results.

WHAT ELSE DO YOU NEED TO KNOW?

If you volunteer to take part in this study, you will be one of about 18 people to do so at the University of Kentucky.

The Markey Cancer Center is providing financial support and/or material for this study.

A description of this clinical trial will be available on ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WILL YOUR INFORMATION (OR SPECIMEN SAMPLES) BE USED FOR FUTURE RESEARCH?

Your information or samples collected for this study will NOT be used or shared for future research studies, even if we remove the identifiable information like your name, medical record number, or date of birth.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

Your health information that may be accessed, used and/or released includes:

- Gender
- Race
- Age
- Results of physical exams, blood tests, X-rays, tumor measurements, tissue analysis and other diagnostic and medical procedures;
- Your medical history, medical information about your disease and medical information pertaining to your condition; and other diagnostic and medical procedures related to the study.
- Information on side affects you may experience and how these were treated;
- Long-term information about your general health status and the status of your disease;
- Medicare Health Insurance Claim Numbers (HICN), Social Security Numbers (SSN) and Employer Identification Numbers (EIN) if regulated by Medicare reporting provisions.

The Researchers may use and share your health information with:

- The University of Kentucky's Institutional Review Board/Office of Research Integrity;
- Law enforcement agencies when required by law;
- University of Kentucky representatives;
- UK Hospital
- Food and Drug Administration (FDA)
- Investigational Drug Service (IDS
- Center for Clinical and Translational Science (CCTS)
- National Cancer Institute (NCI)
- Kentucky Cancer Registry
- Markey Cancer Center
- Your primary physician will be contacted if the researcher, in the course of the project, learns of a medical condition that needs immediate attention.

The researchers agree to only share your health information with the people listed in this document.

Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign this form, it will not affect your:

- Current or future healthcare at the University of Kentucky;
- Current or future payments to the University of Kentucky;
- Ability to enroll in any health plans (if applicable); or
- Eligibility for benefits (if applicable).

After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:

- Send a written letter to: Zin Myint, M.D. University of Kentucky Markey Cancer Center, 800 Rose Street, Lexington, KY 40536 to inform her of your decision.

- Researchers may use and release your health information **already** collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).

You will not be allowed to review the information collected for this research study until after the study is completed. When the study is over, you may have the right to access the information.

The use and sharing of your information has no time limit.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Monday-Friday at (859) 323-1184.

INFORMED CONSENT SIGNATURES

This consent includes the following:

- **Key Information Page**
- **Detailed Consent**

You will receive a copy of this consent form after it has been signed.

_____ **Signature of research subject**	_____ **Date**
_____ **Printed name of research subject**	
_____ Printed name of [authorized] person obtaining informed consent and HIPAA authorization	_____ Date
_____ Signature of Principle Investigator or Sub/Co-Investigator	_____ Date

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is a phase I dose escalation study with expansion cohort. Dose escalation will be determined by a Bayesian optimal interval (BOIN) design [41]. The target DLT rate is 30%. Patients are enrolled in cohorts with 3 patients in each cohort. Enrollment will be temporarily halted after the last patient of each cohort is enrolled until all current patients are DLT evaluable or withdrawn from the study. A patient will be considered DLT evaluable if he completes at least 75% of the planned dose of Epidiolex in the first 30 days of the treatment, unless the reason is due to toxicity.

The primary objective is to evaluate the acute toxicity and long-term safety and tolerability of Epidiolex (CBD) in patients with biochemically recurrent prostate cancer. Acute toxicity of Epidiolex is evaluated through DLT rate, which is calculated as the total number of patients experienced DLTs at a dose level divided by the total number of patients treated at the corresponding dose level. The calculation of DLT rate will only include DLT evaluable patients. Patients who are not DLT-evaluable will not be replaced for the current cohort and will not be included in the calculation of DLT rate. At the end of the dose escalation part of the study, we will use the dose escalation/de-escalation decision rules (see section 9.1.1) to decide the dose level for dose expansion cohort. If the current dose at the end of dose escalation is already the highest available dose, and the decision rules did not indicate de-escalation or elimination, the highest dose level is deemed as safe for acute toxicity; otherwise, the dose recommended by the decision rule is the estimated MTD.

Following dose-escalation, an expansion cohort will be enrolled to confirm safety for acute toxicity, evaluate long-term safety and tolerability and explore evidence of efficacy of the study treatment. Long-term safety and tolerability are evaluated through the summary statistics of adverse events occurred within the 90-day follow-up period in patients who received any amount of study drug. The study treatment is deemed as not safe for long-term tolerability if any of the following criteria are met:

- More than 40% of the patients treated at the dose level selected for expansion cohort experienced grade 3 or higher AEs that are possibly/probably/definitely related to study treatment
- More than 30 % of the patients experienced grade 3 or higher CNS toxicity that are possibly/probably/definitely related to study treatment

9.1.1 Dose Escalation / De-escalation Decision Rule

	Number of patients Treated								
Decision Rule	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Escalate (or highest) if # DLT <=	0	0	0	0	1	1	1	1	2
De-escalate (or lowest) if # DLT >=	1	1	2	2	2	3	3	3	4
Eliminate (or stop) if # DLT >=	--	--	3	3	4	4	5	5	5

Note: the next cohort will be treated at the current dose level if the criteria are not met for escalation/de-escalation rules.

9.1.2 Secondary and Correlative Endpoints

The secondary endpoints include change in serial PSA, PSA velocity and testosterone levels from baseline

throughout the treatment period as an indication of biochemical response and health-related quality of life (as assessed by the EORTC QLQ-C30 and QLQ-PR25).

The correlative endpoint includes CBD receptor 1 and 2 expression levels.

9.2 Sample Size/Accrual Rate

We plan to enroll up to 9 DLT evaluable patients for dose escalation. If 3 or more of the first 9 patients are not evaluable for DLT, additional cohort(s) will be enrolled to ensure at least 9 DLT evaluable patients for dose escalation. Once we have established the highest tolerated dose is deemed as acceptable for acute toxicity or estimated the MTD, we will begin treating 6 to 9 more patients in an expansion cohort to confirm safety for acute toxicity, evaluate long-term tolerability and explore evidence of efficacy of the study treatment. The number of patients to be enrolled in expansion cohort depends on the DLT rate during the dose escalation part of the study. The total planned sample size for this study is 18 (enrolled) patients with about 12 patients treated at the MTD or the highest planned dose.

9.3 Analysis of Primary Endpoint

Dose escalation decisions and MTD are estimated through the rules specified in section 9.1.1. DLT rate at each dose level will be calculated along with the Fisher's exact confidence interval at 95% confidence level. AE, SAE and AE of special interests will be summarized by descriptive statistics to evaluate long-term safety.

9.4 Analysis of Secondary Endpoints

Change in serial PSA, PSA velocity and testosterone levels from baseline throughout the 90-day treatment period will be represented by longitudinal profiles and analyzed by mixed effects model. Baseline is defined as the last non-missing PSA measurement prior to administrating Epidiolex. PSA and testosterone levels may be categorized and summarized by response rates with confidence intervals. Patients who are DLT evaluable, have baseline measurement and have at least one post-baseline measurement will be included in the analysis of secondary endpoints.

The health-related quality of Life (EORTC QLQ-C30 and QLQ-PR25) collected longitudinally will be analyzed using appropriate linear models for repeated measures data.

9.5 Analysis of Correlative Endpoints

Post-hoc analyses will be conducted on correlative endpoints with appropriate statistical methods depending on distribution and availability of collected data.