Document Coversheet

Study Title: Telotristat With Lutathera in Neuroendocrine Tumors

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	4/11/2023
NCT Number:	NCT04543955
IRB Number	61180
Coversheet created:	5/23/2023

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.

PROJECT INFORMATION

0 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-20-GI-114-PMC: Randomized, Parallel Arm, Phase II Study of Telotristat (Xermelo) in Combination with Lutetium Lu 177 Dotatate (Lutathera) in Well Differentiated Neuroendocrine Tumors (NETs)

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-20-GI-114-PMC:Telotristat + Lutathera NET

Anticipated Ending Date of Research Project: 6/30/2034

Maximum number of human subjects (or records/specimens to be reviewed) 12

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 100

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

Study Population: A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design: The inclusion criteria are based on the requirements for patient selection needed to achieve the primary objectives of the study. See attached eligibility criteria. Subject must be 18 years of age or older. The racial composition will reflect the population of Central Kentucky and the patients seen at the Markey Cancer Center: Caucasian: African American: Hispanic: Asian:Native American: 70:20:10:<1:<1 %.

• A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group: No groups are excluded from this study.
• The proposed dates of enrollment (beginning and end): We expect to enroll 70 patients in 30 months.
• A description of proposed outreach programs for recruiting women and minorities in clinical research as subjects: Only the IRB approved procedures in place as described in the "Subject Recruitment Methods & Privacy" section will be used.
• The proposed dates of enrollment will be from 9/1/2020 through 6/30/2034.

See Appendix Eligibility for additional information.

Attachments

Attach Type	File Name
StudyPopulation	Appendix eligibility.pdf

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:				
Latinx:				
Native Hawaiian/Pacific Islander:				
White:				
American Arab/Middle Eastern/North African:				
Indigenous People Around the World:				
More than One Race:				
Unknown or Not Reported:				

If unknown, please explain why:

The racial composition will reflect the population of Central Kentucky and the patients seen at the Markey Cancer Center: Caucasian: African American: Hispanic: Asian: Native American: 70:20:10:<1:<1 %.

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

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]
- 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.

Once a subject is referred for consideration in the study, the subject's history and status will be completely evaluated and treatment recommendations will then be discussed thoroughly with the subject. Any alternative forms of therapy will be presented as objectively as possible. The risks and hazards of the study drugs will be explained to the subject. The Investigator shall seek consent only under circumstances that provide the subject sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject shall be in language understandable to the subject. No informed consent may include any exculpatory language, through which the subject is made to waive or appear to waive any of their legal rights, or releases or appears to release the Investigator, UK, or its agents from liability for negligence. The subject must be able to comprehend the informed consent form and sign prior to subject enrollment. The subject will then receive a signed copy of the consent form.

Informed Consent for Research Involving Emancipated Individuals: N/A
Informed Consent for Research Involving Non-English Speaking Subjects: N/A
Research Repositories: N/A
If a subject participating in a research study has a complaint concerning any aspect of their participation, the subject should notify the study investigator and/or the study coordinator. The complaint will be recorded in the subject's case report binder. The subject will meet with various members of the University of Kentucky Medical Center until their complaint has been resolved. The contact information for the IRB was given to the subject during the informed consent process. The subject will be reminded to contact the IRB to review the patient's rights as a research subject. The complaint and the resolution will be reviewed in the monthly research meeting. The following individuals will review the complaint; the Study P.I., the Study Coordinator, the Research Program Coordinator and the Department Administrator. A plan will be discussed to prevent a similar complaint from occurring, and a final report will be sent to the IRB.

☐ 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.

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).

See attached Appendix Background

Objectives

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

1.1 Primary Objective
1.1.1 To evaluate 20-month PFS for each arm and assess non-inferiority compared to historical controls (i.e., results from the NETTER-1 clinical trial)

1.2 Secondary Objectives:
1.2.1 To determine the overall response rate (ORR) by Response Evaluation Criteria In Solid Tumors (RECIST, v1.1) at 6 and 12-months post initiation of therapy
1.2.2 To establish the safety profiles of the combination of Telotristat (two dose levels, 250 mg PO TID and 500 mg PO TID) and Lutetium Lu 177 Dotatate
1.2.3 To evaluate median Progression-free Survival (PFS)
1.2.4 To evaluate urinary 5- HIAA at baseline and at 12 months
1.2.5 To evaluate quality of life as measured by the QLQ-C30 and QLQ-GI.NET21, two complementary instruments developed by the European Organization for
Research and Treatment of Cancer (EORTC)
1.2.6 To evaluate effect of combination of Telotristat (250mg TID VS. 500mg TID) plus Lu 177 Dotatate on carcinoid syndrome diarrhea and flushing

1.3 Exploratory Objective
1.3.1 Measure the somatostatin receptor uptake on gallium 68 or copper 64 dotatate at baseline and correlate with response

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.

Study Design/Endpoints
This is an open label, randomized, parallel arm, Phase II trial of two dose levels of Telotristat (250 mg TID and 500 mg TID) in combination with Lutetium Lu 177 Dotatate (Lutathera). The primary endpoint of the study is 20-month PFS. The study is designed to test a non-inferiority hypothesis for one proportion (proportion of patients had 20-month progression-free) for each arm separately. No interim analysis will be performed. . All patients will be followed up to 36 months after the study enrollment. An intent-to-treat analysis will be performed and patients who drop-out prior to 20 months of follow-up will be deemed non-evaluable for the primary objective and excluded from primary objective analysis. PFS distribution and median PFS will be estimated using Kaplan-Meier method based

on 36 months follow-up data.

Sample Size/Accrual Rate
A sample of 33 patients per arm will provide 80% power to test a non-inferiority difference of 5% for the combination based on a one-sided test with 5% significance level. Based on the NETTER trial [7], we will assume that PFS rate at 20 months is equal to 65%. We will further assume a small non-inferiority margin of 5% and that the PFS at 20 months with the PRRT (Lutathera)+Telotristat combination is equal to 80%. The assumption in hypothesized effect size of the combination is based on the width of the 95% confidence interval presented in the NETTER trial results. If at least 25 out of 33 patients in each arm progression-free at 20 months, we will conclude that PFS rate at 20 months for the combination (either arm) is non-inferior. To account for a potential 5% drop-out/non-evaluable rate, we will enroll 35 patients per arm. We expect to enroll 2-3 patients per month. Thus, a total of 70 patients requires an accrual duration approximate of 30 months (2.5 years) and study duration approximate of 66 (5.5 years) months (30 months accrual plus 36 months follow-up).

Analysis of Secondary and Exploratory Endpoints
ORR will be assessed by RECIST v1.1 of CT/MRI scans completed at 6 and 12 months post-initiation of study treatment, and will be estimated along with 95% binomial confidence intervals.
Comparison of pre vs. follow-up measurements of urinary 5-HIAA and QOL will be performed using paired t-tests or linear mixed models for repeated measurements. Carcinoid syndrome assessment of diarrhea and flushing will be summarized at each time point of follow-up and paired comparisons will be performed using non-parametric Wilcoxon signed-ranks test or paired test for proportions. Safety data for this combination will be summarized in a descriptive table. All patients who received study drugs will be included in the safety analysis. The maximum grade of toxicity for each AE category of interest will be recorded for each patient and the summary results will be tabulated by category and grade. We will describe all serious (= grade 3) toxicity events on a patient-by-patient basis. Frequency and incidence tables of toxicity and AEs will be generated for each treatment arm.

Analysis of Exploratory Endpoint
Radiographic expression of somatostatin receptors will be summarized using descriptive statistics. Krenning Score from the gallium 68 Dotatate will be summarized by calculating the proportion of patients in each Krenning Score category and exploratory assessments for association with clinical response (ORR) will be performed using Fisher's exact test. Median, interquartile range will be calculated for quantitative image measurements from gallium 68 Dotatate and exploratory comparison of levels with clinical response (ORR) will be performed using two sample t-test or nonparametric analogs. No interim analysis will be performed for the primary clinical endpoint of the trial.

Randomization and Stratification
Permuted block randomization will be generated with a 1:1 allocation ratio for the two treatment arms. A separate randomization list will be generated to account for the stratification factor of tumor grade (Grade 1 and 2). The study statistician will generate the randomization list and incorporated into the clinical trial management system.

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. Initial contact will be made with potential subjects only by those having legitimate access to the subjects' identity and the subjects' information.

Agreeable subjects will then be invited to participate in an informed consent process as described in the Informed Consent Process" section. No advertising will be performed other than that already approved by the IRB: The study will be posted on the web-site of the Markey Cancer Center in the general information list and listed in the Markey Cancer Center quarterly: Clinical Research Newsletter. No advertising is planned at this time. The study will be posted on the web-site of the Markey Cancer Center in the general information list and listed in the Markey Cancer Center quarterly: Clinical Research Newsletter.

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.

All of the procedures to be carried out are illustrated in the attached study calendar.

These experimental procedures include the following: a) obtaining informed consent, b) evaluating for inclusion and exclusion criteria, c) assessing adverse events by infusion center nurse, research nurse, or other qualified healthcare professional and d) recording and using the clinical data outlined in flowcharts to develop the data base for this study.

Additional research procedures include:
-Administration of study drug, Telotristat (Xermelo)
-Data collection via questionnaires: EORTC QLQ-C30 (Core) and QLQ-GI.NET21

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.

The data that will be collected is summarized in the attached Appendix Study Calendar (Research Procedures section).

Attachments

Attach Type	File Name
DataCollection	FINAL pill diary. GI-114. 22JUL2021.pdf

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 and the Markey Precision Medicine Unit with oncology research experience, ranging from one to 20 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.

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.

General Risks

There is a risk that the study drugs may not be as good as the usual approach for your cancer at shrinking or stabilizing the patient's cancer.

Subjects also may have the following discomforts:

• Spending more time in the hospital or doctor's office.
• Be asked sensitive or private questions about things they normally do not discuss.
• May not be able to take part in future studies.

Drug Risks
The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Telotristat Side Effects
Possible Side Effects of Telotristat are listed below and grouped according to which part of the body to which they relate:

Gastrointestinal (relating to the stomach and the intestines)
Very common (in 100 people, more than 10 and up to 100 people may experience):
• Nausea

Common (in 100 people between 1 and 10 may experience):
• Flatulence, abdominal distention, gastrointestinal pain, constipation, abdominal pain/upper and lower abdominal pain

Frequency not reported: Fecaloma (obstruction of the intestine due to fecal blockage)

Nervous system
Very common (in 100 people, more than 10 and up to 100 people may experience):
• Headache

Hepatic (relating to the liver)
Common (in 100 people between 1 and 10 may experience):
• Increased gamma-glutamyltransferase (GGT) levels (may indicate damage to the liver or bile ducts)

Frequency not reported:

• Elevated lab values including alkaline phosphatase, increased alanine aminotransferase, increased aspartate aminotransferase (which may indicate liver damage)

Psychiatric (relating to mental and emotional health)
Common (in 100 people between 1 and 10 may experience):

• Depression

Cardiovascular (relating to heart function)
Common (in 100 people between 1 and 10 may experience):

• Peripheral edema (swelling in your lower legs or hands)

Metabolic (relating to the biochemical processes that regulate the body's functioning)
Common (in 100 people between 1 and 10 may experience):

• Decreased appetite

Other
Common (in 100 people between 1 and 10 may experience):

• Pyrexia (fever)

Possible Side Effects of Lutetium Lu 177 Dotatate (Lutathera):

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Lutetium Lu 177® more than 20 and up to 100 may have:
• Nausea
• Vomiting
• Fatigue

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Lutetium 177® from 4 to 20 may have:
• Diarrhea
• Abdominal Pain
• Decreased appetite
• Headache
• Dizziness
• Hair loss

RARE, AND SERIOUS
In 100 people receiving Lutetium 177®, 3 or fewer may have:
• Muscle pain
• Bone pain
• Leg swelling
• Kidney failure
• Bone marrow failure

Additional Drug Risks
The study drugs used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that subjects check with the study doctor about what types of birth control or pregnancy prevention to use during the study and for 6 months after they have completed the study.

The study drug could interact with other drugs. Rarely, there are problems getting enough supplies of the study drug.

Blood draw risks
Some of the risks from drawing blood from the arm may include pain, bruising, soreness, light-headedness or fainting, bleeding and rarely, infection.

Imaging Risks

The gallium 68 dotatate scan that subjects get in this study will expose them to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called “background radiation.” No one knows for sure whether exposure to these low amounts of radiation is harmful to the body.

Other Risks and Precautions

Lutetium Lu 177 Dotatate, a beta- and gamma particle-emitting pharmaceutical, is a radioactive therapeutic agent. Though the external radiation exposure associated with Lutetium Lu 177 Dotatate is low, care must be used to keep body fluids from coming in contact with family members or caregivers. The study doctor will give subjects information on the good hygiene practices to follow to minimize radiation exposure from bodily fluids to household members and caregivers. Some of the precautions include using disposable gloves when wiping up blood, urine, stools, or vomit, or when handling stained clothes. Clothing soiled with Lutetium Lu 177 Dotatate or fecal matter or urine should be washed promptly and separately from other clothing. Subjects will be advised to use the same toilet each time they use the bathroom in their home, and if possible, use a different toilet than other members of your household. They will also be advised to sit down on the toilet to urinate to keep urine from splashing or spraying. They will be asked to follow these guidelines for at least 30 days after each Lutetium Lu 177 Dotatate treatment. Flush the toilet a few times after each use.

There is always a chance that any medical treatment can be harmful. In addition to risks described in this consent, subjects may experience a previously unknown risk or side effect.
Conventional therapies such as radiation and chemotherapy are not effective in the treatment of neuroendocrine tumors. First-line systemic therapy usually consists of a somatostatin analogue for control of both hormonal secretion and tumor growth. With the exception of Everolimus and Lutetium Lu 177 Dotatate for the treatment of nonfunctional NETs, no standard second-line systemic treatment options are currently available.

Although the clinical benefit of Telotristat and Lutetium Lu 177 Dotatate has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

Radiolabeled somatostatin analogue Lutetium Lu 177 Dotatate is a beta- and gamma-emitting radionuclide. Radiolabeled somatostatin analogues provide a means of delivering targeted radiation with a high therapeutic index to tumors that express somatostatin receptors. Data from nonrandomized trials of Lutetium Lu 177 Dotatate have consistently shown high response rates and long durations of median progression-free survival in heterogeneous patient populations with gastroenteropancreatic neuroendocrine tumors. The NETTER-1 trial validates these early-phase data in the context of a prospective, randomized trial. In summary, Lutetium Lu 177 Dotatate resulted in markedly longer progression-free survival than high-dose octreotide LAR and was associated with limited acute toxic effects in a population of patients who had progressive neuroendocrine tumors that originated in the midgut.

We hypothesize that inhibition of serotonin production will lead to cytostatic effect on neuroendocrine tumors and will complement anti-tumor activity of lutetium 177 dotatate. We anticipate our proposed combination will result in improved treatment efficacy as reflected by improved 20-month PFS as compared to historical control.

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 can get the usual treatment for this type of cancer without being on study. They can participate in another study, if one is available. They can receive only palliative care or refuse all treatment.

The usual approach for patients who are not in a study is treatment with Lutetium Lu 177 Dotatate or everolimus, which are both approved by the Food and Drug Administration (FDA). Everolimus is able to keep the disease stable in 50 out of 100 treated patients for about 11 months. Lutetium Lu 177 Dotatate is able to keep the disease stable in 50 out of 100 treated patients for about 30-35 months.

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

Subject specimens will not be collected for research purposes.

Return of Research Results or Incidental Findings (if applicable): N/A
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 National Institutes of Health, the Food and Drug Administration (FDA), other regulatory agencies, the Institutional Review Board (IRB), and Study Investigators reserve the right to review the study data and medical records relating to this research study. 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. All data stored is on site at UK 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 the study will be evaluated clinically and with standard laboratory tests before and at regular intervals during participation in this study. Safety will be assessed by physical examinations, clinical chemistry, and hematology tests and monitoring of adverse events. Adverse event reporting is mandatory from the date of the first study drug administration through 30 days following the

last dose of the study drug. Adverse events which occur prior to the first study drug administration will be captured in the patient's medical history. Laboratory, vital signs, or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant. The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. Additionally, guidelines for AE's will comply with the University of Kentucky's IRB requirements. Confidentiality of medical information is discussed at length in the informed consent. 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.

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

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 payment for their participation 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 and/or their insurance company, Medicare, or Medicaid will be responsible for the costs of all care and treatment that they would normally receive for any conditions they may have. These are costs that are considered medically necessary and will be part of the care they receive even if they do not take part in this study. Their insurer, Medicare, or Medicaid, may agree to pay for the costs. However, a co-payment or deductible may be needed from them. The amount of this co-payment or deductible may be costly. The University of Kentucky may not be allowed to bill the subject's insurance company, Medicare, or Medicaid for the medical procedures done strictly for research.Therefore, the sponsor, Markey Cancer Center, will pay for procedures done strictly for research, including the data collection via questionnaires: EORTC QLQ-C30 (Core) and QLQ-GI.NET21. The study drug, Telotristat (Xermelo) will be provided by Lexicon Pharmaceuticals, Inc. at no charge to the subject. Subjects will not have to pay for any study procedures.

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 study principal investigator has primary responsibility for monitoring the safe conduct of this study. Additionally, the Markey Cancer Center Quality Assurance Committee (QAC) provides 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 QAC review timeline based on the phase, origination of the study and known safety issues. The members of the QAC 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. All members should view themselves as representing the interest of the study patients and not that of the institution. At each meeting, the following study data is reviewed by the QAC: treatment issues, serious adverse events (SAEs) per FDA's definition, dose levels, dose modifications, and responses as applicable.

The QAC reviews protocols to assure the following:

• progress of the trial and safety of participants,
• compliance with requirements regarding the reporting of severe adverse events,
• that any action resulting in a temporary or permanent suspension of this NIH-funded clinical trial is reported to the responsible NIH grant program director, and
• data accuracy and protocol compliance.

The QAC, the Protocol Review Committee (PRC), the responsible disease-specific Clinical Care and Research Team (CCART)

and/or the UK/VA 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

Back to Top

Future Use and Sharing of Material (e.g., Data/Specimens/Information)

If the material collected for 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:

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).

Dr. Chauhan currently holds an IND for the ongoing "MCC-18-LUN-107-PMC: Phase II study of combination Rucaparib with Nivolumab in platinum sensitive small cell lung carcinoma patients as maintenance after induction therapy with platinum doublet", IND#: 143099.

No sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity.

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:

Telotristat (Xermelo), Lutetium Lu 177 Dotatate (Lutathera)

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:

The FDA is currently reviewing our IND submission which has been assigned IND# 152333. Our IND references Lexicon Pharmaceuticals IND for Telotristat IND# 137916.

IND Submitted/Held by:

Sponsor: ☐		Held By:	
Investigator: ☑		Held By:	Aman Chauhan, MD
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

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 and Lexicon Pharmaceuticals, Inc.

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

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is an open label, randomized, parallel arm, Phase II trial of two dose levels of Telotristat (250 mg TID and 500 mg TID) in combination with Lutetium Lu 177 Dotatate (Lutathera). The primary endpoint of the study is 20-month PFS. The study is designed to test a non-inferiority hypothesis for one proportion (proportion of patients had 20-month progression-free) for each arm separately. No interim analysis will be performed. . All patients will be followed up to 36 months after the study enrollment. An intent-to-treat analysis will be performed and patients who drop-out prior to 20 months of follow-up will be deemed non-evaluable for the primary objective and excluded from primary objective analysis. PFS distribution and median PFS will be estimated using Kaplan-Meier method based on 36 months follow-up data.

9.2 Sample Size/Accrual Rate

A sample of 33 patients per arm will provide 80% power to test a non-inferiority difference of 5% for the combination based on a one-sided test with 5% significance level. Based on the NETTER trial [7], we will assume that PFS rate at 20 months is equal to 65%. We will further assume a small non-inferiority margin of 5% and that the PFS at 20 months with the PRRT (Lutathera)+Telotristat combination is equal to 80%. The assumption in hypothesized effect size of the combination is based on the width of the 95% confidence interval presented in the NETTER trial results. If at least 25 out of 33 patients in each arm progression-free at 20 months, we will conclude that PFS rate at 20 months for the combination (either arm) is non-inferior. To account for a potential 5% drop-out/non-evaluable rate, we will enroll 35 patients per arm. We expect to enroll 2-3 patients per month. Thus, a total of 70 patients requires an accrual duration approximate of 30 months (2.5 years) and study duration approximate of 66 (5.5 years) months (30 months accrual plus 36 months follow-up)

9.3 Analysis of Primary Endpoint

Hypothesis testing based on non-inferiority of PFS rate at 20 months will be performed for each arm using an exact test for one proportion. Furthermore, PFS will be estimated using the Kaplan Meier method and estimates at 20 months, other specific time points and 95% confidence interval will be calculated. Survival analysis models such as Cox regression will also be considered.

An intent-to-treat analysis will be initially performed wherein all patients who received at least one dose of the treatment regimen is included in the analysis. For the primary endpoint of PFS at 20 months, patients who drop-out and are not evaluated for the 20 month time point will be considered non-evaluable. Subjects will be followed for up to 36 months in order to capture significant events and median PFS (secondary endpoint) estimates.

9.4 Analysis of Secondary and Exploratory Endpoints

9.4.1 Analysis of Secondary Endpoints

ORR will be assessed by RECIST v1.1 of CT/MRI scans completed at 6 and 12 months post-initiation of study treatment, and will be estimated along with 95% binomial confidence intervals.

Comparison of pre vs. follow-up measurements of urinary 5-HIAA and QOL will be performed using paired t-tests or linear mixed models for repeated measurements. Carcinoid syndrome assessment of diarrhea and flushing will be summarized at each time point of follow-up and paired comparisons will be performed using non-parametric Wilcoxon signed-ranks test or paired test for proportions.

Safety data for this combination will be summarized in a descriptive table. All patients who received study drugs will be included in the safety analysis. The maximum grade of toxicity for each AE category of interest will be recorded for each patient and the summary results will be tabulated by category and grade. We will describe all serious (≥ grade 3) toxicity events on a patient-by-patient basis. Frequency and incidence tables of toxicity and AEs will be generated for each treatment arm.

9.4.2 Analysis of Exploratory Endpoint

Radiographic expression of somatostatin receptors will be summarized using descriptive statistics. Krenning Score from the gallium 68 Dotatate or copper 64 Dotatate will be summarized by calculating the proportion of patients in each Krenning Score category and exploratory assessments for association with clinical response (ORR) will be performed using Fisher's exact test. Median, interquartile range will be calculated for quantitative image measurements from gallium 68 Dotatate or copper 64 Dotatate and exploratory comparison of levels with clinical response (ORR) will be performedusing two sample t-test or nonparametric analogs.

9.5 Interim Analysis

No interim analysis will be performed for the primary clinical endpoint of the trial.

9.6 Randomization and Stratification

Permuted block randomization will be generated with a 1:1 allocation ratio for the two treatment arms. A separate randomization list will be generated to account for the stratification factor of tumor grade (Grade 1 and 2). The study statistician will generate the randomization list and incorporated into the clinical trial management system.

9.7 Exclusions from Toxicity and Overall Response Rate

9.7.1 Evaluation of Toxicity in Phase 2 Trials

All patients will be evaluable for toxicity from the time of their first treatment with Telotristat.

9.7.2 Evaluation of Response as Secondary Endpoint

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following eight categories:

1) complete response,
2) partial response,
3) stable disease,
4) progressive disease,
5) early death from malignant disease,
6) early death from toxicity,
7) early death because of other cause, or
9) unknown (not assessable, insufficient data*)*

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific but primarily follow RECIST v1.1.

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, *etc.*). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.