UCSF Helen Diller Family Comprehensive Cancer Center

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Fluoroethyltyrosine for the evaluation of intracranial neoplasm (UC-GlioFET)

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Study Drug: Fluoroethyltyrosine (FET)

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Protocol Signature Page

1. I agree to follow this protocol version as approved by the UCSF Protocol Review and Monitoring Committee (PRMC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	Fluoroethyltyrosine (FET) for the evaluation of intracranial neoplasm (UC-GlioFET)
Patient population	Patient population 1: Patients with intracranial neoplasms (glial or metastatic disease) with concern for recurrence or progression on conventional imaging (e.g., MRI). Three sub-populations will be considered: 1. Recurrent metastatic lesions 2. Recurrent high-grade gliomas (Grades 3 and 4) 3. Recurrent low-grade gliomas (Grades 1 and 2) Patient population 2: Patients with suspected glial neoplasms (Grade 2-4) planning to undergo biopsy or surgery prior to primary treatment (radiation therapy and/or surgery)
Rationale for Study	FET accumulates in malignant cells within intracranial neoplasms and can be used to detect recurrent disease and characterize grade of glial neoplasms.
Primary Objectives	1) To determine if FET PET can differentiate between benign treatment- related changes and recurrence in comparison to pathology in population 1 with recurrent metastatic disease and high-grade gliomas. 2) To determine if FET PET can differentiate between low-grade and high- grade gliomas in population 2.
Secondary Objectives	1) To determine if FET PET can differentiate between benign treatment- related changes and recurrence in comparison to pathology or imaging follow-up in population 1. 2) To determine if FET PET can differentiate between benign treatment- related changes and recurrence in comparison to pathology in population 1 with recurrent low-grade gliomas.
Exploratory Objectives	1) To assess relationships between serial FET PET and clinical outcome in population 1 with recurrent metastatic disease and gliomas. 2) To determine if MRI can differentiate between benign treatment-related changes and recurrence.
Study Design	This is a prospective, Phase 2, single center, open-label study in patients with intracranial neoplasms. There is a provision of Stopping Rules for the Pediatric patient population.

Number of patients	199 patients, enrolled over four years. 150 patients will be enrolled in patient population 1 and 49 patients will be enrolled in patient population 2 .

Primary Endpoints	• Imaging endpoint:
	  ○ Reader binary characterization of study as positive for recurrence disease in population 1, and positive for high-grade glial neoplasm in population 2.
	  ○ Intracranial lesion tumor-to-background ratio.
	• Pathology:
	  ○ Presence of tumor and grade of tumor.

Duration of Therapy	The study will involve one imaging study involving FET PET for all patients. Adult patients may undergo repeat FET PET.
Duration of Follow up	Follow-up will be performed to correlate imaging findings with pathology.
Duration of study	The study will reach completion one year after completion of enrollment.
Study Drugs	Fluoroethyltyrosine (FET)
Safety Assessments	Patient vital signs will be taken immediately before and after the administration of the radiopharmaceutical. The patients will also be asked to report adverse events.

List of Abbreviations

AE	adverse event
CHR	Committee on Human Research (UCSF IRB)
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FET	Fluoroethyltyrosine
FN	False Negative
FP	False Positive
HDFCCC	Helen Diller Family Comprehensive Cancer Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug application
IRB	Institutional Review Board
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PET	Positron Emission Tomography
PRC	Protocol Review and Monitoring Committee (UCSF)
RANO	Response Assessment in Neuro-Oncology
ROI	Region of interest
TBR	Tumor-to-brain ratio
TN	True Negative
TP	True Positive

Table of Contents

1 Introduction

1.1 Overview

Imaging using the amino acid-based PET tracer O-(2-[18F]fluoroethyl)-L-tyrosine (FET) is a promising imaging platform for both primary and secondary brain neoplasms. However, widespread incorporation of FET-PET into the routine clinical management of brain tumor patients has not occurred within the United States. The primary issue associated with this promising imaging agent is the lack of approval by the Food and Drug Administration (FDA). The goal of this protocol is to obtain prospective data and the safety and efficacy of FET for the detection of intracranial neoplasms with the goal to submit a New Drug Application (NDA) for this agent. To date we are not aware of an institution on the United States who has previously obtained an IND for FDA or submitted an FDA application. We are aiming to achieve two indications with this study. The first is the ability to accurately detect recurrent disease in patients who have previously undergone surgery and/or radiation. The second indication is the ability to distinguish low-grade glial neoplasms from high-grade glial neoplasms.

1.2 Background

Glial tumors are the most common primary neoplasms affecting the central nervous system. This heterogeneous group of tumors is classified as low or high grade based on histologic features such as the presence of increased cellularity, mitotic activity or necrosis (1). Due to their infiltrative nature, gliomas are rarely cured via surgical resection, contributing to a disproportionately high morbidity and mortality (2,3).

Imaging techniques play an important role in the clinical management of neuro-oncology patients. Anatomic imaging with magnetic resonance imaging (MRI) is the mainstay for initial diagnosis, treatment planning and post-treatment follow-up of brain tumors given its widespread availability, high spatial resolution and excellent soft tissue contrast. However, conventional MRI techniques have several important limitations in brain tumor imaging, including those currently used to define disease progression as part of the RANO criteria (Response Assessment in Neuro-Oncology) (4). Contrast enhancement, a marker of blood-brain barrier permeation, is neither sensitive nor specific for the presence of tumor tissue. The majority of low-grade glial neoplasms do not enhance, while inflammatory processes common in the postsurgical/post treatment setting often enhance avidly. A diagnostic dilemma occurs in up to 30% of patients within the first 12 weeks following completion of chemoradiotherapy, whereby an enlarging area of contrast enhancement on MRI may represent either early tumor progression, which necessitates a change in the ongoing treatment regimen, versus “pseudoprogression”, which represents non-progressive treatment-related change that does not require alteration of the treatment regimen.

Positron-emission tomography (PET), which has the capability to image specific metabolic processes using radiolabeled endogenous molecules, is another imaging modality with high potential for use in neuro-oncology. The most widely used PET tracer is the glucose analogue fluorodeoxyglucose (FDG). However, FDG is not ideal for brain tumor imaging given the high background uptake of normal brain parenchyma and limited specificity in distinguishing between progressive tumor and post-treatment inflammation. O-(2-[18F]fluoroethyl)-L-tyrosine (FET) is an amino acid-based PET tracer with high uptake in brain tumors and relatively low uptake in normal brain parenchyma (5). Various studies have demonstrated the ability of FET-PET to detect recurrent gliomas with higher sensitivity and specificity compared with conventional imaging techniques (6,7). Additionally, the value of using FET-PET tumor grading has also been shown (8).

We believe that FET PET has significant promise in the imaging and characterization of patients with primary and secondary intra-cranial neoplasms. This protocol is intended to focus on the two main applications of the radiotracer in order to obtain the data required for the submission of an NDA application from the FDA.

Of note, we will follow-up patients without histologic correlation in order to determine the accuracy of imaging follow-up as a possible replacement for histology as a marker of disease recurrence. This will be the motivation and goal of the study's secondary objective.

1.3 Patient Population

Patient population 1: Patients with intracranial neoplasms (glial or metastatic disease) with concern for recurrence or progression on conventional imaging (e.g., MRI). This population will be broken into three groups:

1. Recurrent metastatic lesions
2. Recurrent high-grade gliomas (Grades 3 and 4)
3. Recurrent low-grade gliomas (Grades 1 and 2)

Patient population 2: Patients with suspected glial neoplasms (Grade 2-4) planning to undergo biopsy or surgery prior to primary treatment (radiation therapy and/or surgery).

2 Objectives of the Study

2.1 Primary

- To determine if FET PET can differentiate between benign treatment-related changes and recurrence in comparison to pathology in population 1. Two sub-populations will be considered for the primary endpoint:
    - Recurrent metastatic lesions
    - Recurrent high-grade gliomas (Grades 3 and 4)
- To determine if FET PET can accurately differentiate between low-grade and high-grade gliomas in population 2.

2.2 Secondary

- To determine if FET PET can differentiate between benign treatment-related changes and recurrence in comparison to pathology or imaging follow-up in population 1.
- To determine if FET PET can differentiate between benign treatment-related changes and recurrence in comparison to pathology alone in population 1 patients with recurrent low-grade gliomas (Grades 1 and 2).

2.3 Exploratory

- To assess relationships between serial FET PET and clinical outcome (benign treatment-related changes and recurrence) in patients with recurrent metastatic lesion, recurrent high grade gliomas and recurrent low grade gliomas.
- To determine if MRI can differentiate between benign treatment- related changes and recurrence.

2.4 Endpoints

2.4.1 Primary Endpoints

- Imaging endpoint:
    - Reader binary characterization of study as positive for recurrence disease in population 1, and positive for high-grade glial neoplasm in population 2.
    - Intracranial lesion tumor-to-background ratio.
- Pathology:
    - Presence of tumor and grade of tumor.

3 Study Design

3.1 Characteristics

This is a prospective, Phase 2, single center, open-label study in patients with intracranial neoplasms. Eligible participants will undergo baseline assessments at enrollment. All study participants will undergo a single FET PET study. Repeat FET PET will be offered to adult patients and not in pediatric patients.

3.2 Stopping Rules

For pediatric patients, patients will be reviewed after imaging, and if inappropriate patient management is instituted based upon the results of the 18F-FET PET imaging, then we will suspend enrollment of pediatric patients until the case is reviewed with the FDA and the neurooncology site committee.

3.3 Number of Subjects

It is anticipated that 199 patients over four years will be enrolled in this study.

3.4 Eligibility Criteria

Patients must have baseline evaluations performed prior to the administration of the radiopharmaceutical and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Patients participating in other clinical trials will be eligible for this study including patients undergoing surgery guided by 5-aminolevulinic acid.

3.4.1 Inclusion Criteria

1. Presence or suspicion of intracranial neoplasm in two populations:
    a. Population 1: patients after primary treatment (radiation therapy and/or surgery) with suspicion of recurrence on MRI. Three sub-populations will be considered:
        i. Recurrent metastatic lesions

ii. Recurrent high-grade gliomas (Grades 3 and 4)

iii. Recurrent low-grade gliomas (Grades 1 and 2)

b. Population 2: patients prior to primary treatment with planned biopsy or surgical resection.

2. Age > 3 years.

3.4.2 Exclusion Criteria

1. Patient with known incompatibility to PET or CT/MRI scans.
2. Patient unlikely to comply with study procedures, restrictions and requirements and judged by the Investigator to be unsuitable for study participation.
    a. Sedation or anesthesia can be used for patients who cannot tolerate the exam.

3.5 Discontinuation of Study Intervention

Study drug will be given per protocol, unless any of the following discontinuation criteria are met:

- Unacceptable adverse event(s);
- Participant decides to discontinue study drug (with or without concurrent withdrawal of informed consent);
- Significant participant non-compliance with protocol;
- If the participant meets an exclusion criterion (either newly developed or not previously; or, recognized) that precludes further study drug administration.
- General or specific changes in the participant's condition render the participant unacceptable for study drug administration in the judgment of the investigator.

Participants will be discontinued from study drug administration when any of these criteria apply. The reason for discontinuation, and the date the participant discontinued (defined as the later date of decision to discontinue drug or last dose) must be documented in the case report form (CRF). Participants removed from study for unacceptable adverse events will be followed as described in Section 7.3. Participants who do not receive study drug will be replaced.

3.6 Duration of Follow Up

Patients will be in follow-up up until their planned biopsy or surgery is performed to correlate imaging findings with histology. Follow-up will be performed off study, and there are no study specific related procedures that are required after the imaging study. If patients do not undergo biopsy or surgery, we will review imaging that was performed as clinical standard of care to determine if the lesion has grown as part of the secondary aims.

3.7 Study Discontinuation/Withdrawal

Participants will be discontinued/withdrawn from study participation when any of the following criteria apply:

- Completion of study intervention and follow-up per protocol
- Lost to follow-up

- Withdrawal of consent for data submission
- Death
- Study termination

The reason for discontinuing study participation and the off-study date must be documented in the case report form (CRF).

Participants may withdraw from the study at any time and for any reason at their own request or at the request of their legally acceptable representative. Participants will be asked for reason(s) of withdrawal and presence of any AEs for documentation in the CRF. If possible, the participant will be seen and assessed by the Investigator and AEs followed according to protocol.

The study may be terminated early for any reason, which may include, but is not limited to:

- Changes in the benefit-risk assessment
- Decision to stop manufacturing study drug

In the event of early study termination, follow up medical records collection may occur, as described in Section 3.6, for participants who remain on study at that time. Investigators will be notified of any additional steps that are necessary to protect participants' interests. Investigators must notify the IRB and other applicable stakeholders, in accordance with local laws and regulations.

3.8 Study Timeline

3.8.1 Primary Completion

The study will reach primary completion 48 months from the time the study opens to accrual.

3.8.2 Study Completion

The study will reach study completion 60 months from the time the study opens to accrual.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Products

4.1.1 Investigational Drug #1

O-(2-[18F]fluoroethyl)-L-tyrosine (FET) is a radiopharmaceutical that will be produced under cGMP by a research pharmacists certified and highly experienced in the Department of Radiology and Biomedical Engineering.

5 Treatment Plan

5.1 Patient Preparation

Patients will fast for four hours prior to examination as per joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabeled amino acids.

5.2 Dosage and Administration

The imaging agent (FET) will be administered on an outpatient basis. It will be administered intravenously within the PET scanner at the time of imaging. The nominal injected dose will be 4 to 7 mCi ±10% of FET per imaging time point. Pediatric doses will be adjusted based upon the patient's weight (dose = [(patient weight in kg)/70 kg] x adult dose). The maximum dose will be 7 mCi, adjusted by weight.

5.2.1 Other Modalities or Procedures

5.2.1.1 PET Imaging

Participants may undergo sedation as required in order to successfully undergo imaging. Sedation or anesthesia will be administered per institutional protocol.

Study participants will undergo the FET PET imaging after all screening and baseline assessments have been completed. The radiopharmaceutical will be administered while the patient is in the PET scanner, and imaging will last for 40 minutes. Acquired PET data will be reconstructed so that three time points are created:

1. Perfusion: 60-second acquisition that starts immediately when activity is noted in the field of view.
2. Equilibrium: 10-minute acquisition acquired between 10 and 20 minutes after injection.
3. Washout: 10-minute acquisition acquired between 30 and 40 minutes after injection.

Additionally, a 20 minute acquisition will be reconstructed between 20 and 40 minutes after injection to match the analysis performed in Lohmann et al (*8*).

Each study will be reviewed by a board-certified nuclear medicine physician and neuroradiologist within seven working days of the completion of the study, and a formal report will be dictated. This will be performed separately from the final analysis. The imaging findings on FET PET will be provided to the neurosurgeon and can be used in addition to MRI for planning of biopsy and surgery. For patients who received subsequent surgery, if possible the multi-parametric imaging examination will be used to target 1-4 tissue samples that have distinct metabolic findings for distinguishing recurrent disease from treatment effects.

If imaging is performed on a PET/MRI, a gadolinium-based contrast will be administered. The patient's eGFR will be checked and gadolinium will be administered per radiology department guidelines. The MRI protocol will include the clinical standard MRI. The MRI protocol may also contain research sequences such as novel sequences used for attenuation correction on PET/MRI (ie ZTE or zero echo time) and MRI spectroscopy sequences.

Optional repeat FET PET imaging will be offered to adult patients.

5.3 Monitoring and Toxicity Management

Each patient receiving FET will be evaluable for safety. The safety parameters include vital signs (heart rate and blood pressure) as well as physical findings and spontaneous reports of adverse events reported to the investigator by patients.

6 Study Procedures and Observations

Screening assessments must be performed within 30 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

REDCap will be used to collect data for this study. REDCap is a secure, HIPAA-compliant, web-based system.

6.1.1 Treatment Period

- FET administration and adverse event evaluation
    - Evaluation of adverse events 20 min after completion of imaging, ± 60 min
- Vital signs
    - 20 min prior to administration of radiotracer, ± 60 min
    - 20 min after completion of imaging, ± 60 min
- Confirmation of negative pregnancy test (woman of childbearing potential only)

6.1.2 Follow-up

Patients will be followed up clinically to see if they have undergone biopsy or surgical resection. This will be performed based on standard of care and is not a requirement as part of this protocol. For patients who have not had biopsy or surgical resection, we will review imaging studies performed within six months of the FET PET in order to evaluate change in size as part of the secondary aims.

6.1.3 Optional Study Procedures - Imaging

Optional repeat FET PET imaging will be offered to adult patients. Repeat procedures include:

- FET administration and adverse event evaluation
    - Evaluation of adverse events 20 min after completion of imaging, ± 60 min

6.2 Prohibited Medications

There are no prohibited medications.

7 Evaluation of Safety

7.1 Definitions

7.1.1 Evaluable for Toxicity

All patients will be evaluable for toxicity from the time of FET administration.

7.1.2 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.1.3 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.1.4 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.1.5 Unexpected

An adverse event or suspected adverse reaction is considered unexpected if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered unexpected for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

7.1.6 Serious

An adverse event or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.1.7 Life-threatening

An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.2 Recording of an Adverse Event

All grade 3 and above adverse events will be recorded using the NCI CTCAE v4.0. The Investigator will assign attribution of the possible association of the event with use of the investigational drug.

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as none, mild, moderate or severe according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

7.3 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.4 Expedited Reporting

7.4.1 Reporting to the HDFCCC Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the UCSF PI or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

7.4.2 Reporting to Institutional Review Board

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) and the San Francisco VA Medical Center within 5 business days of his/her awareness of the event.

7.4.3 Expedited Reporting to the FDA

If the study is being conducted under an IND, the Sponsor (or the Sponsor-Investigator) is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with federal regulations (21 CFR §312.32).

The Sponsor (or Sponsor-Investigator) must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 7.1.4)
- Unexpected (as defined in 7.1.5)
- Serious (as defined in 7.1.6)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Please see Appendix 2 for further details on the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) policies and procedures.

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

- To determine if FET PET can accurately predict the presence of recurrent tumor in patients previously treated with surgery and/or radiation for population 1, broken down by metastatic disease, high-grade gliomas and low-grade gliomas.
- To determine if FET PET can accurately differentiate between low-grade and high-grade glial neoplasms for population 2.

8.2 Determination of Sample Size and Power Estimate

We will provide a sample size for both populations. We expect that 60% of our patients will be imaged for recurrent disease after surgery and/or radiation therapy, and we expect that 40% of our patients will be imaged prior to initial therapy for glial malignancy.

Population 1: For our primary endpoint we will use a misclassification rate as our statistical endpoint, defined as the percentage of patients that are classified incorrectly as either recurrent disease and treatment related changes (ie misclassification rate = [FP+FN]/[FP+FN+TP+TN]).

- True positive (TP): FET PET read as positive for tumor, pathology/follow-up demonstrates tumor recurrence in at least one biopsy sample.
- False positive (FP): FET PET read as positive for tumor, pathology/follow-up negative tumor recurrence in none of the biopsy samples.
- True negative (TN): FET PET read as negative for tumor, pathology/follow-up negative tumor recurrence in none of the biopsy samples.
- False negative (FN): FET PET read as negative for tumor, pathology/follow-up demonstrates tumor recurrence in at least one biopsy sample.

For our sample size analysis, we will break it down by the three subpopulations:

- Recurrent metastatic disease: We estimate that there will be a prevalence of 65% for recurrent metastatic tumor at time of imaging. Papers that estimate misclassification rate have shown a misclassification rate of 24% (sensitivity of 86.7%, specificity of 68.2%, and a prevalence of 43%) for perfusion MRI (9), a misclassification rate of 46% (sensitivity of 59%, specificity of 41%, and a prevalence of 75%) for lesion quotient MRI. For FET PET, the literature has shown a misclassification rate ranging from 7 to 17%:

- Misclassification rate of 17% with a sensitivity of 83%, specificity of 85% and prevalence of 84% (10).
- Misclassification rate of 7% with a sensitivity of 95%, specificity of 91% and prevalence of 48% (11).

For our sample size analysis, we have used a binomial test for proportions. Assuming a misclassification rate of 35% for conventional MRI and 10% for FET PET, we will need to image 34 patients with pathologic correlation to demonstrate the difference with a significance level of 0.01 with a power of 90%, and a one-sided test. Our null hypothesis is that there is no difference between MRI and FET PET misclassification rates (H_null: MRI_misclass = FET PET misclass = 35%). The alternative hypothesis is that the FET PET misclassification rate is lower (H_alt: FET PET misclass < MRI_misclass = 35%). We estimate that 55% of patients will have pathology as a correlate, and we will replace all patients who do not have pathology within four weeks of imaging to fill our primary endpoint. Therefore the total patient population in population 1 with metastatic lesions will be 62 patients.

- Recurrent high grade glioma (Grade 3 and 4): Based on prior data from UCSF, we anticipate that 70% of patients will have recurrent tumor at the time of imaging (12). Using this same paper as an estimate of misclassification rate using MRI for the characterization of recurrent tumor, results in a sensitivity of 82%, specificity of 76%, prevalence of 70% and a misclassification rate of 19.8%. For FET PET, the first paper to publish the sensitivity and specificity of FET PET was Rachinger et al in 2005; they reported a sensitivity, specificity and misclassification rate of 100%, 93% and 2% respectively (45 patients with a prevalence of 69%) (13). A subsequent paper published in 31 patients, 26 of whom had recurrent tumor, had a sensitivity of 100% and a specificity of 84%, resulting in a misclassification rate of 2.6% (14). A third paper looked at the ability to characterize pseudoprogression after radiochemotherapy all of whom had an enhancing lesion on MRI, demonstrated a sensitivity, specificity and misclassification rate of 100%, 91% and 5% respectively (6). No meta-analysis exists for estimating the accuracy of FET PET, and therefore we have selected 5% as a reasonable goal misclassification rate. Our null hypothesis is that there is no difference between MRI and FET PET misclassification rates (19.8% for MRI and 5% for FET PET). For our sample size analysis, we have used a binomial test for proportions. We will need to image 27 patients with pathologic correlation to demonstrate the difference with a significance level of 0.05 with a power of 80%, and using a one-sided t-test. Our null hypothesis is that there is no difference between MRI and FET PET misclassification rates (H_null: MRI_misclass = FET PET misclass = 19.8%). The alternative hypothesis is that the FET PET misclassification rate is lower (H_alt: FET PET misclass < MRI_misclass = 19.8%). We estimate that 40% of patients will have pathology as a correlate, and we will replace all patients who do not have pathology within four weeks of imaging to fill our primary endpoint. Therefore the total patient population in population 1 with high grade gliomas will be 68 patients.
- Recurrent low-grade glioma (Grade 1 and 2): We are including this population as a secondary endpoint in order to gain information on the role of FET PET in the characterization of low-grade gliomas. We aim to image 20 patients as part of this cohort to obtain preliminary information about the role of FET PET in this population.

Population 2: For population 2 we have also selected a misclassification rate for the characterization of tumor as either low or high grade. Most of the data on the literature for the effectiveness of conventional imaging (MRI) for the classification of disease is reported as

sensitivity and specificities; the best meta-analysis available suggests that MR spectroscopy has a sensitivity of 75% and a specificity of 70% (15). In this meta-analysis of 25 studies, there were 427 low-grade and 802 high-grade tumors, resulting in a prevalence of 65% for high-grade tumors. Assuming a prevalence of 65%, this would imply a misclassification rate of 27% for conventional imaging. Using a recent FET PET article that demonstrated a sensitivity and specificity of 100% and 73% respectively for the characterization of low-grade and high-grade gliomas with a prevalence of 52%, we would estimate a misclassification rate of roughly 13% for FET PET (16). Therefore our target misclassification rate is 13%. Our null hypothesis is that there is no difference between MRI and FET PET misclassification rates (27% for MRI and 13% for FET PET). For our sample size analysis, we have used a binomial test for proportions. We will need to image 49 patients with pathologic correlation to demonstrate the difference with a significance level of 0.05 with a power of 80%, using a one-sided test. Our null hypothesis is that there is no difference between MRI and FET PET misclassification rates (H_null: MRI_misclass = FET PET misclass = 27%). The alternative hypothesis is that the FET PET misclassification rate is lower (H_alt: FET PET misclass < MRI_misclass = 27%).

8.2.1 Accrual Estimates

We estimate that 50 patients with intracranial neoplasms will be enrolled each year, and we estimate that we will enroll 199 patients over the four years of the study.

8.3 Analyses Plans

8.3.1 Analysis Population

There will be two analysis populations. The first population will be patients with intracranial neoplasm (both glial and metastatic disease) previously treated with surgery and/or radiation therapy where there is concern for recurrent disease. The second population will be patients with suspicion or known glial malignancy planning on undergoing biopsy or surgery.

The safety analysis dataset will include all patients who completed initial FET PET imaging per protocol.

The efficacy analysis dataset will include all patients who completed initial FET PET imaging per protocol (repeat FET PET imaging is excluded). FET PET scans that are not readable due to data or scanner errors will be excluded from efficacy analyses.

8.3.2 Analysis of Primary Endpoints

All imaging studies will be reviewed by three nuclear medicine physicians blinded to the patient's history and their pathology. Each physician will undergo a reader-training course that will involve FET PET cases not included in the study reads.

- Population 1: recurrent neoplasm versus treatment related effects. Each of the subpopulations will be treated separately, but the analysis will be identical for the recurrent high-grade glioma and recurrent metastatic lesions.

  Imaging Interpretation for Population 1 will involve 1) qualitative, 2) quantitative, and 3) overall assessments. For each patient, the reader will qualitatively determine the number of lesions present on the study to be characterized. For each lesion, the following will be performed:

  1) Qualitative/Visual Assessment

For each lesion, readers will assess whether the lesion is consistent with recurrence or treatment-related changes.

2) Quantitative Assessment

Quantitative assessments will be performed on transaxial slices showing the highest FET accumulation, as described by Galldiks (6). Quantitative analysis will be performed on the 20-40 minute imaging time point (*8*). First, readers will determine the SUVmean of background normal tissue by marking a large region of interest (ROI) on the contralateral hemisphere in an area of unaffected brain tissue. Second, a volume of interest will be placed around the lesion, and within that volume a threshold segmentation will be performed using a lower limit threshold of background SUVmean x 1.6. Third, a 1.6 cm diameter circular ROI will be centered on the qualitatively hottest portion of FET uptake. TBRmax will be calculated by dividing the SUVmean of the 1.6 cm diameter circular ROI by the SUVmean of background normal tissue. TBRmean will be calculated by dividing the SUVmean of the lesion volume of interest (using the background SUVmean x 1.6 threshold) by the SUVmean of background normal tissue. Lesions will be quantitatively evaluated in a binary fashion as recurrence if TBRmax > 2.3 or treatment-related changes if TBRmax ≤ 2.3. For indeterminate lesions, readers will be allowed to use TBRmean to evaluate for recurrence vs. treatment-related changes. Additionally, the SUVmax of the lesion and the SUVpeak will also be calculated.

3) Overall Assessment

Based on qualitative and quantitative assessments, readers will make an overall determination whether FET uptake is most consistent with recurrence or treatment-related changes. For the imaging interpretation, the overall assessment will be used for determination of positive and negative on FET PET.

Composite Truth Standard

A composite truth standard for recurrence or treatment-related changes will be evaluated for each case, utilizing only pathology reports for the primary endpoint. The composite truth standard will be determined by a panel of physicians independent of the FET images, FET imaging reports or the blinded reads from the FET study.

For analysis of the primary endpoint, only histology will be used to determine the composite truth standard and only patients with available histology will be included. Histology must be performed within four weeks of the FET PET to be considered for evaluation.

- True positive (TP): FET PET read as positive for tumor, pathology demonstrates tumor recurrence in at least one biopsy sample.
- False positive (FP): FET PET read as positive for tumor, pathology negative tumor recurrence in none of the biopsy samples.
- True negative (TN): FET PET read as negative for tumor, pathology negative tumor recurrence in none of the biopsy samples.
- False negative (FN): FET PET read as negative for tumor, pathology demonstrates tumor recurrence in at least one biopsy sample.

- Population 2: low-grade glioma versus high-grade glioma. Low-grade glioma is defined by low uptake of FET on all time-points, or progressive increase in SUVs of the lesion at

each of the three imaging time points during the dynamic PET acquisition. High-grade gliomas have moderate to high uptake on FET and flat SUVs between time point two and three, or decreased SUVs at time point three compared to time point one and two (18,19). Readers will have access only to FET PET images during evaluation and will grade the lesions in a binary fashion as having Grade II glial neoplasms or having Grade III/IV glial neoplasms.

- True positive (TP): FET PET read as positive for Grade III/IV neoplasm, pathology demonstrates Grade III/IV neoplasm.
- False positive (FP): FET PET read as positive for Grade III/IV neoplasm, pathology demonstrates Grade II neoplasm.
- True negative (TN): FET PET read as positive for Grade II neoplasm, pathology demonstrates Grade II neoplasm.
- False negative (FN): FET PET read as positive for Grade II neoplasm, pathology demonstrates Grade III/IV neoplasm.

For each population, misclassification rate, sensitivity, specificity, positive predictive value, negative predictive value and accuracy will be calculated for the detection of recurrence (population 1) or Grade III/IV neoplasm (population 2). 95% percent confidence intervals will be created. Inter-reader variability will be calculated for both populations using the kappa statistic.

8.3.3 Analysis of Secondary Endpoints

Secondary endpoint 1: Using the same imaging interpretation described for the primary analysis above, the secondary analysis will include patients with available histology (performed within 4 weeks of FET scans) or follow-up imaging (performed within 6 months of FET scan).

A composite truth standard for recurrence or treatment-related changes will be evaluated for each case. In the absence of pathology, the composite truth standard will use available clinical information to make a determination. Positive for tumor recurrence on follow-up imaging will be based on RANO criteria[4] reads. Follow-up imaging has to be performed within six months of the FET PET imaging study to be considered for evaluation. Additionally, the composite truth standard may consider tumor board notes and subsequent management of the patient to make a determination.

- True positive (TP): FET PET read as positive for tumor, pathology/follow-up demonstrates tumor recurrence.
- False positive (FP): FET PET read as positive for tumor, pathology/follow-up negative tumor recurrence.
- True negative (TN): FET PET read as negative for tumor, pathology/follow-up negative tumor recurrence.
- False negative (FN): FET PET read as negative for tumor, pathology/follow-up demonstrates tumor recurrence.

Secondary endpoint 2: Using the same criteria as described in the primary endpoints we will determine the misclassification rate, sensitivity, specificity, positive predictive value, negative predictive value and accuracy for FET PET in the evaluation of recurrence of low-grade gliomas.

8.3.4 Exploratory Analysis

Exploratory analysis will be performed on patients with glioma who are under suspicion for progression or recurrence. For these participants, standard-of-care MRI performed during the FET PET/MRI will undergo retrospective analysis by a panel of three blinded independent neuroradiologists. The neuroradiologists will classify the findings as positive (indicating recurrence) or negative (indicating treatment-related changes) and compare them with the composite standard of truth. The 3 readers will be blind to 18F-FET PET images, prior imaging results, clinical data, surgical reports, and histopathological results.

Exploratory analysis will also be performed to assess relationships between serial FET PET and clinical outcome (benign treatment-related changes and recurrence) in patients with recurrent metastatic lesion, recurrent high grade gliomas and recurrent low grade gliomas (Population 1).

8.4 Inter-Reader Variability

Fleiss' kappa statistic will be used to determine the agreement between the assessment of FET-PET tumor targeting (tracer uptake in target lesion: yes/ no), as assessed by three independent blinded readers.

8.5 Intra-Reader variability

The percent of agreement between the two interpretations will be computed for each reader. Cohen's kappa statistics will be used to determine the reproducibility of the assessment by individual readers when analyzing the same data repeatedly.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to participants before any protocol related procedures are performed on any participants.

The PI must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the FDA has determined that the study is exempt from IND requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR

approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB -approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10 Protection of Human Subjects

10.1 Protection of Privacy

Participants will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the participant's medical records, and each participant will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendix 1 Schedule of Study Procedures and Assessments

Schedule of Study Procedures and Assessments				
Period/ Procedure	**Screening** (Day -30 to Day 1)	**Imaging** (Day 1)	**Follow-up** (Off-Study, Until biopsy, resection, or imaging)	**Imaging**[1] (Day 30+)
Informed consent	X			
Pregnancy test (women of childbearing potential only)		X		X
Vital signs		X[2]		
Imaging Procedure				
FET administration		X		X
Sedation/anesthesia*		X		X
PET imaging		X		X
Adverse event reporting		X[3]		X[3]
Follow-up				
Correlation with pathology, imaging			X	

*sedation and anesthesia will be administered only in patients where it is required

[1] Optional study procedure

[2] Evaluation of vital signs 20 min prior to administration of radiotracer (± 60 min) and 20 min after completion of imaging (± 60 min)

[3] Evaluation of adverse events 20 min after completion of imaging (± 60 min)

Appendix 2 Data and Safety Monitoring Plan a Non-therapeutic Institutional Trial

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Annual auditing
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the status of each participant is discussed and documented in the site committee minutes.

For “greater than minimal risk” nontherapeutic trials, the assigned DSMC Senior Monitor/Auditor will audit three of the enrolled participants once per year, with a maximum of ten participant charts audited during the entire course of auditing this trial until IRB closure.

If blood or tissue banking trials are determined to be “greater than minimal risk”, then only Serious Adverse Events (SAEs) recorded in OnCore will be reviewed at each DSMC meeting for these trials.

After completion of each auditing visit, the DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 10 enrolled participants have been audited. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered expected or unexpected and whether or not considered associated with the study intervention or procedure, will be entered into OnCore®, UCSF’s Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to study intervention or procedure. Attribution categories are:

- **Definite** – clearly related to the study intervention or procedure.
- **Probable** – likely related to study intervention or procedure.
- **Possible** – may be related to study intervention or procedure.
- **Unrelated** – clearly not related to the study intervention or procedure.

All clinically significant adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study

* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore, as well as submitted to the IRB. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore.

If a death occurs during the treatment phase of the study and is determined to be possibly, probably, or definitely related either to the study intervention or procedure, the Investigator or his/her designee must notify the DSMC Chair or Vice Chair and DSMC Director within one business day.

3.3 Review of Adverse Event Rates

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting requirements.

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