NCT# 03764007

18F-Fluorocholine for the Detection of Parathyroid Adenomas

Protocol Number: IRB# 16-19297
Study Drug: 18F-fluorocholine

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Protocol Signature Page

Protocol No.: 16-19297 **Version Date:** 25MAR2019

1. I agree to follow this protocol version as approved by the UCSF Institutional Review Board (IRB).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. 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	18F-Fluorocholine for the Detection of Parathyroid Adenomas
Patient population	Patients with primary hyperparathyroidism.
Rationale for Study	Based on the promise shown in the preliminary results of these FCH PET pilot studies, we propose to evaluate this modality in a larger, appropriately powered prospective study. Specifically, we propose to conduct a large prospective study comparing the accuracy of US and MIBI with FCH PET (with either low-dose CT or MRI) as first-line imaging modalities in patients with HPT. We believe that this more robust study design will provide more rigorous evidence on the true accuracy and added value of FCH PET for parathyroid localization.
Primary Objective	To investigate the performance (accuracy) of 18F-fluorocholine PET in the detection of hyperfunctioning parathyroid glands in surgical patients with biochemically proven primary hyperparathyroidism.
Study Design	This is a single arm Phase III study evaluating the accuracy of 18F-fluorocholine for the detection of parathyroid adenomas.
Number of patients	140 patients.
Duration of Therapy	Patients will receive a single dose of 18F-Fluorocholine.
Duration of Follow up	Patients will be followed-up off study to determine if they undergo a parathyroidectomy.
Duration of study	The study will reach completion five years from the time the study opens to accrual.
Study Drugs	18F-fluorocholine.
Safety Assessments	Patient reported adverse events during the day of imaging will be recorded.
Efficacy Assessments	The 18F-fluorocholine PET studies will be interpreted by three blinded readers, and the reads will be correlated with pathology at time of parathyroidectomy to determine the accuracy of 18F-fluorocholine PET to detect the location of an abnormal parathyroid adenoma. Additionally, the accuracy of 18F-fluorocholine will be compared to sestamibi when available.

List of Abbreviations

AE	adverse event
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DSMP	Data and Safety Monitoring Plan
FCH	18F-fluorocholine
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
MRI	magnetic resonance imaging
PET	positron emission tomography
PK	pharmacokinetics
PTH	parathyroid
SD	standard deviation
SPECT	Single photon emission computed tomography

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1 Introduction

There is significant clinical need for new superior imaging techniques to localize parathyroid adenomas in patients with primary hyperparathyroidism. Adequate preoperative imaging is vital for successful minimal invasive parathyroidectomy, the standard of care for these patients. F18-Choline PET has shown to accurately localize parathyroid adenomas in selected patients with negative conventional imaging. A larger comparative study is now necessary before this scan can be introduced in the standard work up of these patients.

1.1 Background

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, with an incidence of around 45 per 100,000 person years (1). PHPT is characterized by autonomous hypersecretion of parathyroid hormone (PTH) by one or more parathyroid glands, leading to an elevated serum calcium concentration. Hypercalcemia can cause a wide variety of well-described symptoms ranging from constipation to osteoporosis and also increases the risk of mortality resulting from cardiovascular disease (2). Diagnosis is typically established biochemically, with the finding of a relatively elevated serum calcium level with a concomitant inappropriately-elevated PTH level. In over 80% of cases, PHPT is caused by a single parathyroid adenoma. The remainder of other causes includes multigland disease (either multiple adenomas or 4-gland hyperplasia) and very rarely parathyroid carcinoma (3). Surgery is currently the only method of definitive cure as well as the most effective treatment modality overall. Most patients with PHPT are surgical candidates, but particularly if they are symptomatic or younger than 50 years of age (4). In the majority of cases, the method of surgical intervention has shifted over the past 2 decades, evolving from extensive bilateral neck exploration to a more minimally invasive parathyroidectomy (MIP) approach (5). MIP has been made possible by improvements in preoperative imaging studies that are able to accurately identify (localize) the abnormal gland(s), which in turn have allowed surgeons to perform limited, targeted explorations, with its attendant benefits to shorter operative time, lower complication rate, and smaller incision length (2). Most centers including UCSF routinely perform a combination of neck ultrasound and Tc-99-sestamibi scan (with or without fusion SPECT-CT) for first-time, non-reoperative cases. The diagnostic value of single photon emission computed tomography (SPECT/CT) in predicting the localization of the adenoma has been proven to be the best imaging modality in comparison to normal SPECT, dual-phase planar scintigraphy and subtraction scintigraphy (6-8). However, even SPECT/CT fails to identify the gland in up to 30% of the cases (9). These cases mandate the traditional bilateral neck exploration, with its abovementioned attendant disadvantages compared to MIP.

1.2 18F-fluorocholine for parathyroid adenomas

Recently, a case report was published describing a potential new imaging modality for patients with pHPT. Quak et al. reported the incidental finding of a parathyroid adenoma using 18F-Fluorocholine (FCH) PET-CT in a patient suspected of recurrence of prostate cancer (10). Choline is part of the phospholipid layer in the cell membrane; it is hypothesized that hyperfunctioning parathyroid cells have an increased activity of the phospholipid/Ca2+-dependent protein kinase which would lead to increased choline uptake and in turn greater imaging accuracy of PET detection with radiolabeled choline such as FC (11). Since then three studies with preliminary results have been published showing a superior detecting rate of FCH PET-CT over different types of conventional imaging in both patients with PHPT and secondary hyperparathyroidism (12-14). Although these initial results with FC have been encouraging, the total body of evidence is still very small and more research is needed.

1.3 Preliminary Data

At our institution, we are completing a prospective pilot-study in which the feasibility of choline PET as a second-line imaging modality is investigated. Only patients with negative or discordant US and MIBI are enrolled. After FCH PET, patients undergo surgery and have biochemical follow up to compare the accuracy of localization. So far 8 patients have been scanned, all of whom have shown a distinctly positive finding on PET scan (Figure 1). In all eight patients who have undergone surgery, the offending parathyroid adenomas were identified intraoperative at exactly the location indicated by PET with biochemical cure confirmed at follow-up.

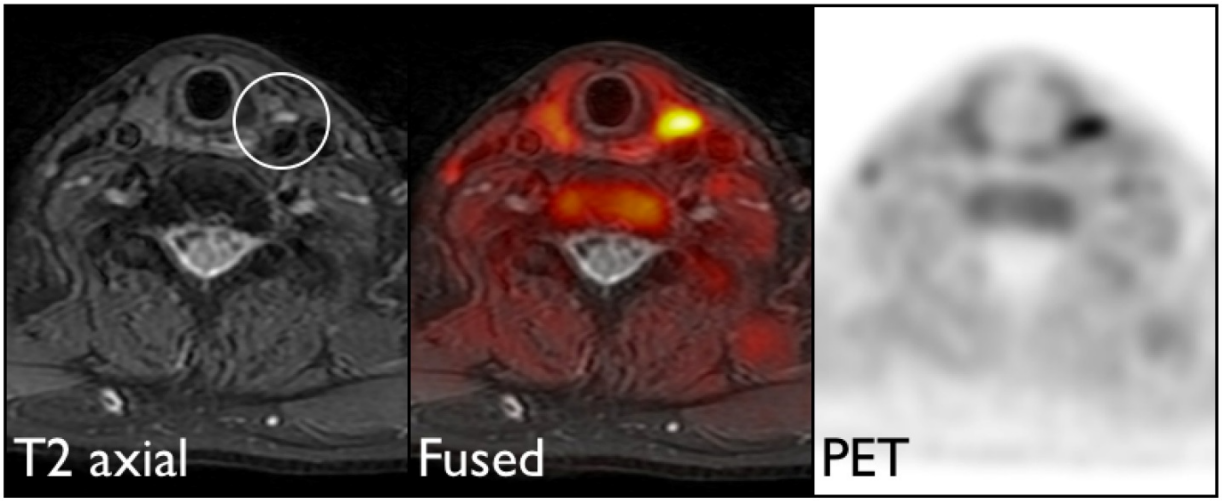

Figure 1: T2 image, FCH PET image, and fused FCH PET/MRI image in a patient with pHPT and negative MIBI. A clear focus of tracer uptake is noted posterior ot the left thyroid with associated T2 hyperintense nodule, consistent with a parathyroid adenoma. On surgical exploration this was found to be a parathyroid adenoma.

1.4 Rationale for the Proposed Study

Based on the promise shown in the preliminary results of these FCH PET pilot studies, we propose to evaluate this modality in a larger, appropriately powered prospective study. Specifically, we propose to conduct a large prospective study comparing the accuracy of US and MIBI with FCH PET (with either low-dose CT or MRI) as first-line imaging modalities in patients with HPT. We believe that this more robust study design will provide more rigorous evidence on the true accuracy and added value of FCH PET for parathyroid localization.

2 Objectives of the Study

2.1 Primary objective

To investigate the performance (accuracy) of 18F-fluorocholine PET in the detection of hyperfunctioning parathyroid glands in surgical patients with biochemically proven primary hyperparathyroidism.

3 Study Endpoints

3.1 Primary endpoint 1

Sensitivity and specificity of 18F-fluorocholine PET for the detection of abnormal parathyroid adenomas confirmed by pathology as compared to sestamibi imaging.

3.2 Primary endpoint 2

Sensitivity and specificity of 18F-fluorocholine PET for the detection of abnormal parathyroid adenomas confirmed by pathology as compared to a predefined threshold.

3.3 Secondary endpoint

Detection rate of 18F-fluorocholine PET in patients who have not undergone surgical resection.

4 Study Design

4.1 Characteristics

This is a prospective single arm single center Phase III study evaluating the ability of 18F-fluorocholine to detect the location of parathyroid adenomas.

4.2 Number of Subjects

A total of 140 patients will be enrolled in this study.

4.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug 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.

4.3.1 Inclusion Criteria

1. Age ≥ 13 years.
2. Biochemically proven hyperparathyroidism and an indication for surgery.
3. Ability to understand a written informed consent document, and the willingness to sign it.

4.3.2 Exclusion Criteria

1. Pregnancy.
2. Patients unlikely to comply with study procedures, restrictions and requirements and judged by the Investigator to be unsuitable for study participation.

4.4 Duration of Study

Patients will undergo a single imaging study using 18F-fluorocholine. Study related procedures will end after the study visit. Patients who undergo subsequent parathyroidectomy, will have their results reviewed and compared to the results from the imaging study.

4.5 Study Timeline

140 patients over five years are expected to enroll, with an expected enrollment of 28 patients per year.

5 Study Drugs

5.1.1 Investigational Drug: 18F-fluorocholine

18F-fluorocholine will be synthesized by the UCSF cyclotron facility under GMP conditions.

6 Administration Plan

6.1 Dosage and Administration

All patients will receive a one-time injection of 18F-fluorocholine of 4-7 mCi.

6.2 Monitoring and Toxicity Management

Each patient receiving 18F-fluorocholine will be evaluable for safety. The safety parameters include spontaneous reports of adverse events reported to the investigator by patients.

Each patient will be assessed after the administration of 18F-fluorocholine for the development of any toxicity. Toxicity will be assessed according to the NCI CTCAE v4.0.

7 Study Procedures and Observations

7.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Section 6 Schedule of Study Procedures and Assessments. Screening assessments must be performed within 60 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. All on-study visit procedures are allowed **a window of ± 5 days** unless otherwise noted. 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.

7.1.1 Pre-Imaging Period

7.1.1.1 Screening Assessments (Day -60 to Day 1)

The Screening assessments must be completed within 60 days of the Day 1 Visit. Patients will not be required to have undergone US or sestamibi imaging prior to FCH PET.

- Written informed consent will be obtained prior to performing any study related activities.
- Inclusion/exclusion criteria will be checked.

7.1.2 Imaging Period

7.1.2.1 Study Procedures (Day 1)

- Administration of 18F-fluorocholine
    - The one-time nominal injected dose will be 4 to 7 mCi containing FCH. Patient shall begin imaging between 20 and 60 minutes after the injection of the radiopharmaceutical.
- Imaging using either PET/CT or PET/MRI
    - Coverage for the scan will extend from the base of the skull to the pulmonary artery. PET acquisition will be for a minimum of 10 minutes per bed position.
    - A dictated report will be made of the imaging findings and be provided to the endocrine surgeons. FCH PET imaging results will be used in conjunction with other imaging modalities, including available ultrasound and sestamibi studies, to direct surgical intervention.

7.1.3 Long Term Follow-up Procedure

Patients will be followed-up off protocol for up to one year. For patients who subsequently undergo parathyroidectomy, the determination of biochemical cure will proceed per the usual standard of care, including the use of intraoperative PTH (IOPTH) measurements, and calcium and PTH measurements in the postoperative setting at standardized intervals. Biochemical cure will be documented if the 2-4 week postoperative serum calcium and PTH levels drop both in comparison to preoperative values as well as to normal ranges. In addition, the final pathological diagnosis will be recorded for comparison purposes.

8 Reporting and Documentation of Results

8.1 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.0 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events.

8.2 Definitions of Adverse Events

8.2.1 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.

8.2.2 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.

8.2.2.1 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.

8.2.2.2 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.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

8.2.2.3 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.

8.2.2.4 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.

8.3 Recording of an Adverse Event

Data about these events and their severity 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

8.4 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.

8.5 Adverse Events Monitoring

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Institutional Review Board (IRB); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

8.6 Expedited Reporting

Reporting to UCSF Institutional Review Board

The Principal Investigator must report events meeting the UCSF IRB definition of “Unanticipated Problem” (UP) within 5 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, 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 Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

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)).

9 Statistical Considerations and Evaluation of Results

9.1 Statistical Design

We will enroll a total of 140 patients (65 in our initial cohort, on which the sample size estimate is based). The sample size will be based upon comparison to setamibi SPECT (MIBI). Multiple meta-analysis of MIBI SPECT have been performed and demonstrate a sensitivity ranging 79 to 84% for MIBI SPECT (15,16). This detection rate is higher than we see at our institution since we are a referral center for patients who have previously failed parathyroidectomy, where the study has a lower sensitivity. For the purpose of our analysis we will do our sample size assuming a sensitivity of 70%, which mirrors our practice. At an 87% power with an alpha level of 0.05, we estimate that a sample size of 65 patients would be needed, assuming 100% disease prevalence, 70% accuracy of MIBI (sestamibi), an estimated 85% accuracy of FCH PET, and 10% dropout rate.

9.2 Analyses Plans

At the time of the imaging study, each scan will be interpreted by a nuclear medicine physician, who will be fully cognizant of the clinical, imaging and laboratory data. Focal uptake on choline PET will be reported by location (left/right, location with respect to the thyroid, or description of location if atypical), along with measured SUVmax. These reads will not be used for evaluation of the primary endpoint.

9.2.1 18F-fluorocholine blinded reads

All 18F-fluorocholine imaging data will be anonymized and collected. PET data will be interpreted by three different board certified nuclear medicine readers in a random order at separate reading sessions. Prior to interpretation a training data set using choline PET studies not included in the study will be used to train the readers. Clinical information will not be available to the readers at time of interpretation. Cross sectional imaging from the PET will be available for anatomic correlate, but no other imaging study will be available. Each study will be characterized by location (left/right, location with respect to the thyroid, or description of location if atypical). "Atypical" refers to adenomas that are not in the thyroid bed and would include the mediastinum. All suspected lesions as well as the single most suspicious lesion will be recorded. For example, in the setting of multiple parathyroid adenomas, one lesion will be reported by the readers as most suspicious.

The location of each adenoma that is surgically confirmed will be marked in the identical fashion (left/right, location with respect to the thyroid [ie inferior or superior], or description of location if atypical). For each reader, lesions will be characterized as follows:

1. True positive: Location of the suspected adenoma on FCH PET correlates with location of an abnormal parathyroid at time of surgery. For a patient with multiple hyperplastic glands, only one gland needs to correlate for the patient to count as a true positive.
    a. For analysis, adenomas described as arising in the mid thyroid bed will considered correct if located in either the inferior or superior bed.
2. False positive: Location of the suspected adenoma on FCH PET does not agree with location of an abnormal parathyroid at time of surgery.
3. True negative: There are no true negatives as patients with primary hyperparathyroidism have near 100% incidence of hyperplastic adenomas.
4. False negative: No evidence of parathyroid adenoma on FCH PET independent of findings at time of surgery.

9.2.2 Sestamibi evaluation

In patients who had a sestamibi study performed prior to the fluorocholine imaging study, we will use the original dictated report from the sestamibi. This will be done as there may be significant bias in the interpretation of the sestamibi studies if re-interpreted. Identical to the PET data, the study reports, will be used to characterized location (left/right, location with respect to the thyroid, or description of location if atypical). All suspected lesions as well as the single most suspicious lesion will be recorded. The sensitivity from this analysis will be used as our comparator for the FCH PET. For each reader, lesions will be characterized as follows:

1. True positive: Location of the suspected adenoma on sestamibi correlates with location of an abnormal parathyroid at time of surgery. For a patient with multiple hyperplastic glands, only one gland needs to correlate for the patient to count as a true positive.
    a. For analysis, adenomas described as arising in the mid thyroid bed will considered correct if located in either the inferior or superior bed.
2. False positive: Location of the suspected adenoma on sestamibi does not agree with location of an abnormal parathyroid at time of surgery.
3. True negative: There are no true negatives as patients with primary hyperparathyroidism have near 100% incidence of hyperplastic adenomas.
4. False negative: No evidence of parathyroid adenoma on sestamibi independent of findings at time of surgery.

The performance of the imaging modalities will be quantified by sensitivity, specificity, positive predictive value and negative predictive value.

Performance will be assessed using surgery as the gold standard with postoperative normalization of calcium as the study endpoint as described above. For this study to have a positive outcome, two of the three FCH PET readers have to have a sensitivity that is 10% greater than that of sestamibi imaging. For statistical analysis we will use the McNemars's test with a p-value of 0.05 for significance. We will also compare the sensitivity of 18F-fluorocholine to the predetermined detection sensitivity of 70%. Again, two of the three FCH PET readers have to have a sensitivity that is 10% greater than 70% (ie 80%). We will also report an interreader variability for the FCH PET reads using a Fleiss's Kappa. The baseline characteristics will be reported as follows: continuous parametric data will be reported as mean

+/- standard deviation, continuous non-parametric data as medians with interquartile range. Dichotomous data will be reported as proportions. Patients with missing imaging results or missing data on the primary endpoint will be excluded from the study.

In patients who do not subsequently undergo parathyroidectomy, we will use the dictated reports to determine the detection sensitive for parathyroid adenomas.

9.3 Evaluation of Safety

Analyses will be performed for all patients having received at 18F-fluorocholine. The study will use the NCI CTCAE v4.0.

10 Study Management

10.1 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 Investigator 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 subjects before any protocol related procedures are performed on any subjects.

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 Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator 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.

10.2 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 Institutional Review Board. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

10.3 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.

10.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, 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 the IRB 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 IRB approval. In this circumstance, however, the Investigator must then notify the IRB 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.

10.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

10.6 Case Report Forms (CRFs)

The Principal Investigator and/or their designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

10.7 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and medical records, such as progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

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Appendix 1 Schedule of Study Procedures and Assessments

	Screening (Day -60 to Day 1)	**Imaging** (Day 1)	**Follow-up (off study)** (Day 2 to Day 365)
Informed Consent	X		
Inclusion & Exclusion Criteria Reviewed	X		
Injection of 18F-fluorocholine		X	
PET imaging - PET/MRI or PET/CT		X	
Adverse event reporting		X	
Clinical follow-up for parathyroidectomy results			X

Appendix 2 UCSF Policy/Procedure for Required Regulatory Documents for UCSF Investigator-Initiated Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Clinical Trials where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iRIS.

Procedures

1. Essential Regulatory Documents

Documents Filed in iRIS:

- IRB approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- IRB approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to IRB with supporting fax documentation

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges