



Investigatory New Drug
Clinical Trial Protocol:
Choline C11 Injection

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This document contains the Protocols for the two separate study arms of NCT02260817.

The Protocol for *Expanded Access to ^{11}C choline PET/CT and ^{11}C choline PET/MR for Staging of Recurrent Prostate Cancer with Comparison Study of CT and MR modalities* may be found at pages 2-34

The Protocol for *Expanded Access to ^{11}C choline PET/CT/MR for Staging of Recurrent Prostate Cancer* may be found at page 35-59.



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Clinical Study Protocol Title Page

Study Title: Expanded Access to ^{11}C choline PET/CT and ^{11}C choline PET/MR for Staging of Recurrent Prostate Cancer with Comparison Study of CT and MR modalities.

Test Drug: Choline C11 Injection

Indication Studied: Prostate Cancer Recurrence

Sponsor: Zevacor Molecular

IND No.: 123448

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Confidentiality Statement



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a. INDEX OF ACRONYMS AND DEFINITIONS

ACR	American College of Radiology
AE	Adverse Effect
ANDA	Abbreviated New Drug Application (FDA submission for approval of generic drugs)
CCI	Cancer Care Institute (Affiliate of Illinois Health & Science)
CFR	Code of Federal Regulations (Legal requirements administered by the FDA)
cGMP	Current Good Manufacturing Practices
CRF	Case Report Forms (Patient study records captured in the study database)
CT	Computed Tomography (Imaging system)
DMH	Decatur Memorial Hospital (Affiliate of Illinois Health & Science)
ECOG	Eastern Cooperative Oncology Group (Cancer rating system)
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
IC	Informed Consent
IND	Investigatory New Drug (Application for a clinical trial of an unapproved drug)
IRB	Institutional Review Board
MR	Magnetic Resonance (Imaging system)
NCCN	National Comprehensive Cancer Network
PET	Positron Emission Tomography (Imaging system)
PSA	Prostate-Specific Antigen (Prostate cancer blood test)
SAE	Severe Adverse Effect
SPECT	Single Photon Emission Computed Tomography (Imaging system)
Tc	Technetium (radioactive isotope used as an imaging drug product)
USP-NF	United States Pharmacopeia – National Formulary



1. INTRODUCTION

1.1 Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in American men, and the second leading cause of cancer death. Statisticians at the National Cancer Institute estimate that there will be 233,000 new cases of prostate cancer and 29,480 deaths from prostate cancer in 2014 (seer.cancer.gov/statfacts/html/prost.html). Since the prostate specific antigen (PSA) test became commercially available in 1985, most prostate cancers have been discovered through PSA screening. Widespread PSA screening for prostate cancer has resulted in a migration to a lower stage of prostate cancer. For example, rates of lymph node metastasis at diagnosis have declined from 20% in the 1970s and 1980s to less than 4% today. Imaging to detect the presence and location of metastatic prostate cancer has historically relied on the ^{99m}Tc -MDP bone scan and cross-sectional imaging with a CT scan or MRI. In addition to imaging studies, nomograms based on clinical T stage, PSA level, PSA kinetics, Gleason grade, and volume of cancer in biopsy specimens are used to predict the risk of metastasis (Stephenson AJ, Sacrdino, PT, Eastham, JA et al., 2006). More recently, positron emission tomography (PET) using radiopharmaceuticals such as ^{11}C -choline and ^{11}C -acetate has improved detection of metastatic prostate cancer.

1.2 Prostate Cancer Imaging

1.2.1 Relapsed Prostate Cancer

A rising PSA occurs in approximately 20 to 40% of patients within 10 years of definitive treatment of prostate cancer and is known as a biochemical relapse. A biochemical relapse of prostate cancer usually precedes evidence of relapse using conventional imaging. The definition of biochemical relapse after radical prostatectomy is a PSA of 0.2 ng/mL confirmed at that level or a higher level on a subsequent PSA test 3 months later (Cookson MS, Aus G, Burnett AL, et al, 2007). The definition of biochemical relapse after radiation therapy is a PSA level 2 ng/mL above the nadir level after treatment (Roach M, Hanks GE, Thames H, et al, 2006). PSA kinetics, most commonly the PSA doubling time; the initial stage and grade of prostate cancer; and time from treatment to biochemical relapse can be used to predict localized versus metastatic cancer states. However, early identification on imaging studies of relapsed prostate cancer is essential in treatment planning. Results of studies using ^{11}C -choline PET/CT and ^{11}C -acetate PET/CT have shown high sensitivity and specificity at low PSA levels in men with biochemical relapse after primary treatment for prostate cancer.

Two early studies have shown that ^{11}C -acetate PET is more sensitive than ^{18}F -FDG PET in detection of relapsed prostate cancer (Oyama N, Akino H, Kanamaru H, et al, 2002; Fricke E, Machtens S, Hofmann M, et al, 2003). In a study ^{11}C -choline PET/CT in 41 patients with biochemical relapse after radical prostatectomy sensitivity was 89% with PSA levels < 2.5 ng/mL (Rinnab L, Simon J, Hautmann



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RE, et al, 2009). In a larger study of 190 patients with biochemical relapse after radical prostatectomy, ^{11}C -choline PET/CT detection of prostate cancer was correlated with the PSA level (known as the trigger PSA) and with PSA kinetics. Trigger PSA levels were significantly different between PET-positive and PET-negative patients ($P=0.0001$), and ROC analysis showed an optimal trigger PSA cutoff value of 2.43 ng/mL. Using multivariable analysis, trigger PSA and PSA velocity were independent prediction factors for a positive PET, whereas PSA doubling time was an independent factor for a positive PET scan only in patients with a trigger PSA < 2.0 ng/mL. An important finding of this study was that Gleason grade, pathologic tumor stage and lymph node status, and time from radical prostatectomy to biochemical relapse were not independent prediction factors for a positive PET (Castellucci, P, Fuccio C, Nanni C, et al, 2009).

In a retrospective review reported by the Mayo Clinic, 176 patients with biochemical relapse of prostate cancer after primary treatment underwent ^{11}C -choline PET/CT imaging. Lesions were identified in 32% of the patients by ^{11}C -choline PET/CT which were not detected by conventional imaging. Investigators reported an optimal trigger PSA level 2.0 ng/mL. In this study, a true positive scan was confirmed by pathology of targeted biopsies or of surgical specimens (41.4%), or by conventional imaging. Performance characteristics were sensitivity 93%, specificity 76%, positive predictive value 91% and negative predictive value 81%. This study was limited by the retrospective nature of the data collection and the investigators recognized that prospective studies are needed to compare ^{11}C -choline PET to conventional imaging with bone scan, CT and pelvic MRI (Mitchell, C, Lowe V, Rangel L, et al, 2013).

The choline analog tracer ^{18}F -FCH has been studied in patients with biochemical relapse of prostate cancer with less favorable results than ^{11}C -choline. In a study of 100 patients with biochemical relapse, 89% of patients with trigger PSA < 4 ng/mL were PET negative (Cimitan M, Bortolus R, Morassut S, et al, 2006). In a subsequent study using ^{18}F -FCH in 56 patients with biochemical relapse after radical prostatectomy, sensitivity was 44% when the trigger PSA ranged from 1 to 4 ng/mL (Pelosi E, Arena V, Skanjeti A, et al, 2008).

As ^{11}C -choline has emerged as a favorable diagnostic agent in patients with prostate cancer relapse, studies have been initiated to determine the best imaging modality. ^{11}C -choline PET/CT was compared with ^{11}C -choline PET/MRI in 31 with biochemical relapse. The detection rate for localized relapse was higher and more conclusive for PET/MR which detected 17 regions in 12 patients compared to PET/CT which detected 12 regions in 8 patients. Similar improvements of using MR were also found in detection of lymph node metastases and bone metastases (Eiber M., Souvatzoglou M., Maurer T., et al, 2013).



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1.3 Rationale for Study

Studies of molecular imaging in patients with prostate cancer have shown the following:

1. ^{11}C -choline, ^{18}F -fluorocholine (^{18}F -FCH), and ^{11}C -acetate have shown greater accuracy in prostate cancer staging than conventional imaging or ^{18}F -FDG PET.
2. ^{11}C -choline PET and whole body MRI are complementary, and when combined have the highest sensitivity and specificity in detection of prostate cancer metastasis.
3. ^{11}C -choline has the highest sensitivity at low PSA levels for detection of prostate cancer in men who have a biochemical relapse after primary treatment.
4. ^{11}C -choline PET/CT and PET/MRI are complementary and show the highest sensitivity and specificity in detection of lymph node metastasis when combined.

In patients with biochemical relapse of prostate cancer after primary treatment, early localization of cancer with molecular imaging using ^{11}C -choline PET/CT and PET/MRI can lead to improved treatment planning with observation, local-regional therapy, or with systemic therapy. Molecular imaging using PET drug products and PET imaging techniques have the potential to change the paradigm for treating men with biochemical relapse after radical prostatectomy. In a study of 72 men with biochemical relapse and ^{11}C -choline PET/CT positive lymph node metastasis, salvage lymphadenectomy resulted in a 5-year relapse-free survival of 35% and cancer-specific survival of 75% (Rigatti P, Suardi N, Briganti, A, et al, 2011). Response to treatment can be monitored with PET molecular imaging as well as with PSA, which may lead to earlier additional therapy.

In March 2013, the FDA approved the New Drug Application (NDA) of the Mayo Clinic in Rochester, MN, for the use of ^{11}C -choline as a radiopharmaceutical agent for PET imaging of patients with suspected prostate cancer relapse. ^{11}C -choline has a half-life of 20 minutes, which limits the distribution of the product to Rochester, MN, and the surrounding area. As a result, this diagnostic agent and its associated benefits have limited availability to patients.

The key objective of this study is to provide expanded access to this drug product as currently defined under the reference listed drug label as an investigational drug in geographical service areas where ^{11}C -choline is not available. Under the current label, ^{11}C -choline is approved for use in conjunction with both CT and MR imaging modalities. However, sufficient data does not exist to determine which modality is most efficacious and under what conditions. It is the intention of the study sponsor to image each patient using GE's Trimodality Imaging System that combines PET, CT, and MR techniques to provide PET/CT and PET/MR fused images. As a result, the patient will benefit from the most useful and deterministic imaging information.



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2. STUDY OBJECTIVES

Based on these rationales, this clinical trial will address the following objectives:

- A. Provide expanded access the drug ^{11}C -choline.
- B. Determine the performance characteristics (sensitivity, specificity, positive predictive value, negative predictive value) of ^{11}C -choline PET/CT and PET/MRI in the detection of metastatic prostate cancer in patients with biochemical relapse of prostate cancer after primary treatment in a prospective manner.
- C. Determine the optimal PSA trigger value in ^{11}C -choline PET/CT and PET/MRI positive patients through a prospective study.
- D. Determine factors that predict a confirmed positive ^{11}C -choline PET/CT and PET/MRI using a multivariable analysis of clinical and pathologic data collected prospectively.
- E. Compare the individual performance characteristics of ^{11}C -choline PET/CT and ^{11}C -choline PET/MRI and the combination of ^{11}C -choline PET/CT and PET/MRI

3. ETHICS

3.1 Institutional Review Board

An Investigational Review Board (IRB) will assess and approve the Investigatory New Drug (IND) application. This will include approval of the IND Protocol, Investigator's Brochure, and the Informed Consent. The Principal Investigator and Sponsor will provide the IRB with appropriate reports on the progress of the study, including safety updates, in accordance with applicable FDA regulations and in agreement with policy defined by sponsor and as outlined in this protocol. All amendments to the study will be sent to the IRB for information (minor amendment) or for approval (major amendment) before implementation of the study amendments.

Decatur Memorial Hospital (DMH) and the Cancer Care Institute (CCI, an affiliate of DMH) are both located in Decatur, Illinois. The Decatur Memorial Hospital Institutional Review Board (DMH IRB) will be involved in all aspects of study planning and considerations as per 21 CFR part 56. The DMH IRB is covered under Decatur Memorial Hospital's Federal Wide Assurance (FWA) # of 00006097. The DMH IRB reviews research projects which involve human participants to ensure that two broad standards are upheld: first, that participants are not placed at undue risk; second, that they give un-coerced, informed consent to their participation.



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3.2 Ethical Conduct of Study

The study shall be performed in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations, Food and Drug Administration (FDA) Good Clinical Practice (GCP) regulations as defined within the Code of Federal Regulations, 21 CFR parts 50, 56, and 312 and clinical safety data management (E2A) regulations. The Principal Investigator / Sponsor shall provide the IRB with all relevant material, including copies of the IND protocol, Informed Consent, Investigator's Brochure and any subject information or advertising materials. The study shall not be initiated until the IRB provides written approval of the protocol and the informed consent.

Each study subject shall be required to provide written authorization that their patient information can be disclosed and used by the Principal Investigator and other researchers as well as the Sponsor for the purposes of assessing the efficacy of the study drug and imaging protocol.

3.3 Patient Information and Informed Consent

In compliance with the requirements set forth by the FDA in 21 CFR Part 50, a properly written and executed Informed Consent shall be obtained from each study subject prior to enrollment and initial screening evaluations required by this protocol. The IC has been reviewed by the Sponsor for acceptability and shall be presented by the Principal Investigator, together with the IND protocol and Investigator's Brochure, to the IRB for review and approval prior to the start of the study. The IC shall be written in such a way as to be fully comprehensible by the prospective study participant.

The Informed Consent shall be revised in the event new information becomes available during the study that may be relevant to the subject. Any revision shall be submitted to the IRB for review and approval before use.

It is the Principal Investigator's responsibility to obtain a properly written and executed Informed Consent from the study subject only after there has been an adequate explanation of the goals, methods, anticipated benefits and potential hazards of the study. The subject shall be given ample time to inquire about details of the study and decide whether to participate in the study. The IRB-approved IC shall be signed and dated by the subject and by the person conducting the informed consent discussion. A copy of the properly executed IC shall be provided to the study subject. The original signed informed consent shall be kept in a confidential location on site.



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4. STUDY PATIENTS

4.1 Patient Study Population

Decatur Memorial Hospital (DMH), a not-for-profit division of Illinois Health & Science, will be the site designated for imaging the study subjects and evaluating the ^{11}C -choline PET/CT and PET/MR imaging data. Patients will be referred from within the institution as well as from outside treatment organizations. Urology, radiation oncology and medical oncology practices within an approximately 300 mile radius of the DMH imaging center will be contacted for enrollment of patients into this study. As such, this study will encompass patients being served in major cities, such as Chicago, St. Louis, Cincinnati, Louisville and Indianapolis who would otherwise have to seek ^{11}C -choline PET imaging at the Mayo Clinic in Rochester, MN. In the event that patients outside of the recruitment area wish to enroll in the clinical trial, they will also be considered. A primary source for patients will also be from The Cancer Care Institute, also a not-for-profit division of Illinois Health & Science. This phase III study is planned to provide expanded access to as many patients who elect to participate in the study that are over the age 18 and have experienced a biochemical relapse of prostate cancer after primary treatment.

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria:

1. For biochemical relapse after primary treatment
 - a. PSA ≥ 0.2 ng/ml after radical prostatectomy confirmed at that level or higher on a subsequent test 3 months later
 - b. PSA increase ≥ 2 ng/ml from nadir following radiation therapy
 - c. PSA increase ≥ 2 ng/ml from nadir following radiation therapy plus androgen deprivation therapy with nadir defined with normalized testosterone level
 - d. Two consecutive PSA increases from nadir level after androgen blockade or androgen suppression therapy
2. Kidney function with GFR ≥ 60 mL/sec/1.73m² and Creatinine < 1.7 mg, collected within 90 days of planned scan
 - a. if GFR is $>$ or equal to 60 mL/sec/1.73m², PET/CT will be completed with contrast
 - b. if GFR is < 60 mL/sec/1.73m², PET/CT will be completed without contrast
 - c. if Creatinine is $>$ than 1.7 mg, Radiology will follow ACR recommendations as outlined in department policy
3. No known allergy to iodinated radiologic contrast media
4. Able to have MRI based on screening evaluation



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if patient is found to be MRI incompatible, the ¹¹C-choline PET/MRI portion of the study will not be completed. These patients will not be included in the comparison data, but will have access to ¹¹C-choline PET/CT scan.

5. ECOG Performance Status of 0, 1, or 2

4.1.2 Exclusion Criteria

Patients will be excluded if any of the following criteria are met:

1. ECOG Performance Status > 2.
2. Concurrent malignancy, i.e. colon cancer.
3. Treatment for another malignancy except superficial skin cancer within 5 years

4.2 Subject Withdrawal And Replacement

4.2.1 Criteria For Subject Withdrawal

Subject participation may be withdrawn / discontinued for the following reasons (but not limited to):

1. Patient request for any reason to discontinue participation within the clinical trial.
2. Patient non-compliance with the accepted protocol.
3. Suspension or discontinuation of the clinical trial by the Sponsor, Zevacor Molecular.

4.2.2 Procedures for Subject Withdrawal

Study patients who decide to discontinue the protocol and withdraw from the clinical trial will be seen and assessed by an Investigator. The reason(s) for the withdrawal and the date of the withdrawal will be documented in the study records for the patient.

If death is the reason for the withdrawal from the clinical trial, there are two options for categorizing as such: 1) progressive disease, or 2) a Serious Adverse Event (SAE). Although more than one SAE may be documented as reason for withdrawal, only one SAE will be documented as the cause of death.

At withdrawal, all on-going study-related AEs and SAEs must be followed until resolution, unless in the Investigator's opinion the condition is unlikely to be resolved due to the patient's underlying disease.

5. INVESTIGATIONAL PLAN

5.1 Study Protocol

1. The study will consist of patients who have a biochemical relapse or other evidence of relapse after primary treatment. This study group will consist of patients who have been treated with radiation therapy, or androgen suppression and radiation therapy who have a PSA \geq 2 ng/mL higher than the nadir level. The nadir level in patients who have been treated with androgen suppression and radiation therapy is determined after the serum testosterone level has normalized. This study group will also consist of patients who have been treated with radical prostatectomy and who have a biochemical relapse defined as a PSA of 0.2 ng/mL confirmed at that level or higher on a subsequent PSA test 3 months later. This group may consist of men who have other clinical evidence of relapse such as a suspicious bone scan or CT scan regardless of PSA kinetics. Patients identified as potential subjects will be screened against the eligibility criteria as defined above in Section 4.1.
2. Informed consent will be obtained from all participants before any study related procedures are conducted. Each participant will be informed about the nature of the study, its purpose, and possible risks. Informed consent will be documented by using the written informed consent document approved by the local IRB at the Decatur Memorial Hospital.
3. At the time of referral, patients will be asked to bring their prior records as it pertains to their prostate cancer history. Data collected from outside records, such as radiographic studies, previous imaging studies and biopsies will be incorporated into the study record.
4. Abstracted data for the study record will include:
 - a. Patient demographics such as age, race, and family history of prostate cancer
 - b. Risk factors such as finasteride or dutasteride use, and environmental exposure
(eg. Agent orange)
 - b. Prostate exam results, most recent within last 90 days
 - c. PSA test results, most current and past
 - d. Past medical and surgical history
 - e. Current medications
 - f. Allergies
 - g. Pathology reports
 - h. Imaging reports
 - i. Date of diagnosis
 - j. Date(s) of biochemical relapse and coordinating PSA results

Once all records have been assessed for eligibility, an order for the ^{11}C -choline PET CT scan and MRI scan will be requested from the referring physician and patient will be scheduled and given the appropriate prep instructions.

5. Patients entered into the study will undergo a ^{11}C -choline PET CT scan and MRI scan. The CT scan will be performed with intravenous contrast unless deemed unsafe by lab values. The CT and MRI images will be evaluated for evidence of metastatic prostate cancer. The ^{11}C -choline PET CT and MRI images will be evaluated for evidence of metastatic prostate cancer. Unequivocal evidence of metastasis on both conventional imaging and ^{11}C -choline PET will be considered a true positive. Evidence of metastasis on conventional imaging or ^{11}C -choline PET will be confirmed with biopsy or surgical pathology when possible, or by response to treatment on subsequent imaging. If confirmation of metastasis is not achievable by biopsy or surgical pathology, then confirmation will be achieved with ^{11}C -choline PET CT and MRI images obtained 3 months after treatment conclusion. Rates of confirmed metastasis between conventional CT and MRI images will be compared with the ^{11}C -choline PET CT and MRI images.
6. Upon conclusion of each imaging protocol, the referring physician will receive written documentation of the results. At this time, the patient will be considered off study and no further follow up is required.

5.2 Imaging Protocols - ^{11}C Choline PET/CT/MRI

1. ^{11}C choline PET/CT Imaging Protocol:
 - Patient should hydrate with 16 ounces of water prior to the imaging study
 - Fasting is required for at least 6 hours
 - Void prior to study
 - 15 - 20 mCi ^{11}C -choline IV Injection
 - 5 min delay after injection.
 - PET images skull base to mid thigh with 3 min per bed position
 - Image acquisition order changed due to bladder filling
 - If CT before MRI, then images obtained top to bottom
 - If MRI before CT, then images obtained bottom to top
 - CT skull base to mid thigh for attenuation correction
 - Use of IV contrast, if applicable, based on ACR IV contrast guidelines renal function screening protocol
 - Slice thickness 2.5, kvp 120, mA 100, exposure time 500, 80 - 100 cc contrast
 - Fusion of PET and CT images

2. MRI whole body imaging protocol:
 - No IV contrast
 - High resolution axial T2 prostate bed, axial DWI pelvis, coronal T2 skull base to mid thighs
 - Fusion of coronal and PET images

5.3 Imaging Technology

The imaging studies referenced above will be conducted as defined in Section 5.2 above. The CT and MR studies must be performed as one continuous procedure using the GE Trimodality PET Imaging System. This will require the patient to be immobile for approximately 60 minutes as each imaging study is executed.

The GE Trimodality PET Imaging System consists of the following integrated equipment: GE Discovery PET/CT 7.0 Imaging System, a GE Discovery MR750w 3.0T Imaging System, and the Lateral Docking Trimodality Patient Transporter. This system will allow for the combined imaging of PET, CT, and MR modalities in one integrated session using the Lateral Docking Transporter to ensure image synchronization between the modalities.

5.4 Imaging Review and Interpretations

5.4.1 Image Review

There will be two aspects to the evaluation, interpretation and use of the imaging data that is produced as part of this study. First, the information will be used immediately by the primary treatment physician to best assess the patient's status and select a therapy regimen. Second, at the end of the study, all of the patient data will be gathered for a comprehensive review which will proceed as follows:

1. Each patient will be assigned a research participant number at the time of consent.
2. This participant number will be substituted for all patient identifying information, where possible.
3. Any remaining patient identification information will be scrubbed from the patient files.
4. The patient identifier key will be stored on a password protected computer at DMH.
5. Access to this identifier key will be restricted from any of the data reviewers.
6. Scrubbed patient images with the identifier will be saved to a compact disc for radiologist review.
7. Studies will be presented in a random order for analysis.

8. The imaging studies will be interpreted by board certified radiologists:
 - a. Dr. M. Muscato
 - b. Dr. J. Locke
 - c. Dr. A. Zorn
9. Worksheets will be saved in a locked cabinet at DMH. The worksheets will be scanned and added to the secure computer study database.
10. The imaging reviews will be compared to the histological data or post-treatment imaging data for statistical analysis.

5.4.2 Image Assessment Criteria

The following image criteria will be documented with each patient study utilizing the worksheets included as attachments in appendix A3.0.

- Lesion considered positive if there is focal uptake greater than background.
- Faint uptake within inguinal nodes considered normal.
- Retroperitoneal lymph nodes >1 cm in short axis diameter considered positive.
- Record CT abdomen and pelvis as follows:
 1. Report mass within prostate or prostate bed
 2. Report retroperitoneal lymph nodes with >1 cm short-axis measurement
 3. Report bone metastases
 4. Report any other metastatic disease (liver, lung, etc)
- Record PET/CT as follows:
 1. Study quality (adequate, non-diagnostic)
 2. Positive lymph nodes.
 - Pelvic or retroperitoneal lymph nodes >1 cm.
 - Radiotracer uptake in lymph node any size
 3. Bone metastases
 - Radiotracer uptake
 - CT abnormality
 4. Other metastatic disease (liver, lung, etc.)
 - Radiotracer uptake
 - CT abnormality
 5. Confidence of diagnosis: 3 – 1
(Rating: 3 – Definitely Present, 2 – Probably Present, 1 – Equivocal)
- Record PET/MRI:
 1. Study quality (adequate, non-diagnostic)
 2. Positive lymph nodes.

- Retroperitoneal lymph nodes >1 cm.
- Radiotracer uptake any size lymph node
- DWI positive
- 3. Bone metastases
 - Radiotracer uptake
 - T2 or DWI positive
- 4. Other metastatic disease (liver, lung, etc.)
 - Radiotracer uptake
 - T2 or DWI positive
- 5. Confidence of diagnosis: 3 – 1
(Rating: 3 – Definitely Present, 2 – Probably Present, 1 – Equivocal)

5.5 Study Data – Statistical Analysis

- Sample Size:

This study is designed to compare fused ¹¹C-choline PET/CT and MRI scans against a standard CT scan and MRI scan. Based on the literature, the group detection rates are approximately 50%. In this study a 20 percentage point increase (eg: from 15 – 35 percent) in detection rate is the desired goal. The study is a paired design, in that each procedure will be performed on each individual. The important performance characteristics of these tests, including sensitivity, specificity, positive predictive value, and negative predictive value will be examined within this study. A sample size estimate was derived using a p-value of 0.05, a power of 80 %, and a paired chi square test for proportions. It was further assumed that the false positive rate is about 4 % and the false negative rate is about 20 %, which are similar to the literature. This would indicate approximately 66 pairs of data. To compare, an independent chi square test would indicate about 71 subjects per group for a comparable 20 point change. Increasing the sample size by 10 percent, for attrition, would increase the number of paired samples to about 73. Increasing the number of pairs to 100 will provide some flexibility on the false positive and false negative rates.

While more than 100 patients may be admitted into the study under expanded access, for the purposes of the comparison study and resulting data analysis, only the first 100 qualified patients will be admitted into the study and included in the study data.

- Data Analysis:

1. True positives will consist of evidence of metastatic prostate cancer on conventional CT or MRI images or on ¹¹C-choline PET/CT or MRI images confirmed with biopsy, surgical

pathology, or by response to treatment with androgen suppression or other medical or radiation therapy.

2. True negatives will consist of negative images.
3. False positive will consist of evidence of metastatic prostate cancer on conventional CT or MRI images or on ^{11}C -choline PET/CT or MRI images, but without corresponding confirmation from biopsy, surgical pathology or response to treatment.
4. False negative will consist of negative images, but with positive biopsy, surgical pathology or a response to treatment.
5. Sensitivity, specificity, PPV, and NPV of CT and MRI and of ^{11}C -choline PET/CT and MRI will be calculated
6. Performance characteristics between ^{11}C -choline PET/CT and PET/MRI will be compared.
7. The optimal PSA trigger value in ^{11}C -choline PET/CT and PET/MRI positive patients will be calculated.
8. Demographic, clinical, and pathologic factors that predict a positive ^{11}C -choline PET/CT or PET/MRI will be determined through a multivariable analysis.

5.6 Publishing the Study Data

Upon completion of the clinical study, it is the intention of the Investigators and Study Sponsor to report the performance characteristics (sensitivity, specificity, positive predictive value, negative predictive value) of ^{11}C -choline PET/CT and PET/MRI in the detection of metastatic prostate cancer in patients with biochemical relapse of prostate cancer after primary treatment in a prospective manner and compare to the performance characteristics with those of conventional imaging. We will also report the performance characteristics of ^{11}C -choline PET/CT compared to ^{11}C -choline PET/MRI and the combination of ^{11}C -choline PET/CT and PET/MRI. Finally, we will report the demographic, clinical, and pathologic factors that predict a positive ^{11}C -choline PET/CT or PET/MRI in the two study groups.

6.0 CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

6.1 Contraindications

None

6.2 Warnings and Precautions

- Imaging errors have been reported during previous clinical studies with ^{11}C -choline PET and PET/CT imaging. A negative image does not rule out the presence of recurrent prostate cancer and a positive image does not confirm the presence of recurrent cancer. ^{11}C -choline uptake is not specific



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for prostate cancer and may occur with other types of cancer, such as lung carcinoma and brain tumors.

- Blood PSA levels < 2 ng/mL have been associated with poor performance ^{11}C -choline PET imaging, with indications of higher numbers of false positive and false negative results.
- Tissue inflammation as well as prostatic hyperplasia have been associated with false positive ^{11}C -choline PET images.
- Concomitant colchicine or androgen-deprivation therapeutic drugs, such as luteinizing hormone-releasing analogs and anti-androgen drugs, may interfere with ^{11}C -choline PET imaging. One published report of ^{18}F methylcholine PET imaging indicated that discontinuation of colchicine for two weeks resolved the colchicine effect. The impact of discontinuation of androgen-deprivations therapy upon ^{11}C -choline PET imaging has not been established.

6.3 Limitation of Use

^{11}C -choline PET imaging is NOT a replacement for histologic verification of relapsed prostate cancer.

7. ASSESSMENT OF SAFETY

7.1 Radiation Safety – Drug Handling

^{11}C -choline is a radioactive drug and will be handled with appropriate safety measures to minimize radiation exposure during administration. The use of waterproof gloves and effective shielding when handling ^{11}C -choline will be required. Radiopharmaceuticals, such as ^{11}C -choline will only be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radioactive materials, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

^{11}C -choline will be delivered to a Certified Nuclear Medicine Technician (CNMT) or equivalently qualified personnel in individual, single dose syringes contained within a NRC/DOT approved syringe shield specifically designed for minimizing radiation exposure during handling. The safe handling of Radioactive Material will be as defined within the Sponsors' radioactive material license issued by the Illinois Energy Management Agency (IEMA), the state nuclear regulatory agency responsible for radioactive material within the State of Illinois.



7.2 Radiation Risks – Patients

¹¹C-choline contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Safe handling should be ensured to minimize radiation exposure to the patient.

7.3 Indications and Usage

¹¹C-choline is a radioactive diagnostic agent initially approved for use by the U.S. Food & Drug Administration in 2012 for positron emission tomography (PET) imaging of patients with suspected prostate cancer relapse and non-informative bone scintigraphy computed tomography. It is dispensed and administered under the reference listed drug (RLD) label: 233155. For the purposes of this study, ¹¹C-choline will be produced, dispensed and administered according to the prescribing information as detailed in the approved drug labeling.

7.4 Patient Safety Evaluations

Patient safety will be evaluated prior to participation in the study and before execution of each of the imaging protocols by screening process.

7.5 Safety Review

An Institutional Review Board (IRB) will review the protocol of this study for safety and effectiveness prior to its implementation. The IRB will convene to approve the Clinical Protocol as defined in this document as well as the Informed Consent, as defined in the U.S. Code of Federal Regulations, 21 CFR 50 and 56. The IRB will also meet on an as needed basis to examine any potential safety issues and the overall conduct of the trial.

8.0 ADVERSE REACTIONS

8.1 Adverse Reactions, General

Exclusive of an uncommon, mild injection site reaction, no adverse reactions to ¹¹C-choline have been reported.

8.2 Allergic Reactions

As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency



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resuscitation equipment and personnel will be immediately available during and within a reasonable time soon after the imaging procedures defined in the clinical protocol.

8.3 IND Safety Reporting Requirements

8.3.1 21 CFR 312

The U.S. Code of Federal Regulations, section 21 CFR 312, defines the conditions within which Adverse Events (AE) and Severe Adverse Events (SAE) are reported to the FDA. For the purposes of this study, the sponsor will be responsible for reporting AEs and SAEs to the FDA as defined by these regulations.

8.3.2 Adverse Events

Adverse Event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event, also referred to as an adverse experience, can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality.

An adverse event may be any of the following:

1. A new illness
2. An exacerbation or a sign or symptom of the underlying condition under treatment or of a concomitant illness
3. Unrelated to participation in the clinical study or an effect of the study radiopharmaceutical or comparator drug
4. A combination of 1 or more of the above factors

An exacerbation of a pre-existing condition/illness is defined as a more frequent occurrence or as an increase in the severity of the pre-existing condition/illness during the study. Planned or elective surgical procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during planned or elective surgery is an AE. Conditions leading to unplanned surgical procedures may be AEs.



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The period of observation for collection of (treatment-emergent) AEs extends from the time the subject takes the first dose of study radiopharmaceutical until their exit from the study. The patient will be called within 24 hours after the protocol scan to assess any AEs and SAEs.

In the event of an adverse event, the Investigator is required to file an Adverse Event Report using the AE Report Form to the sponsor within a reasonable period of time, but no later than 3 days after the event has been recognized by the Investigator. The Sponsor contact information for reporting AEs is listed in section 8.3.7 below.

8.3.3 Suspected Adverse Reactions

Suspected Adverse Reaction means 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' means 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 adverse reaction, which means any adverse event caused by a drug.

It is the responsibility of the Sponsor to determine whether the Adverse Event should be classified as a Suspected Adverse Reaction.

8.3.4 Serious Adverse Events (SAEs)

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
- a 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 functions
- a congenital anomaly/birth defect

Important medical events that may not result in death, be 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.



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In the event of an SAE, the Investigator is required to file an Adverse Event Report using the AE Report Form to the sponsor within 24 hours of the Investigator's recognition of the SAE. The Sponsor contact information for reporting AEs is listed in section 8.3.7 below.

8.3.5 Unexpected Adverse Events

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "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.

8.3.6 Submission of IND Safety Reports

The sponsor must report in an IND safety report any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the sponsor needs to ensure that the event meets all three of the definitions:

- Suspected adverse reaction
- Serious
- Unexpected

If the Sponsor concludes that there is a significant likelihood that the imaging drug caused the adverse event, an IND Safety Report will be submitted to the FDA. In the event that the AE is found to be unexpected, fatal, or life-threatening, the sponsor is required to notify FDA and all participating investigators by fax or phone within 7 calendar days of the initial receipt of information. A written IND safety report must follow within 15 calendar days. All other AEs that are found to be causal to the imaging agent and are unexpected must be submitted in writing within 15 calendar days.

Each participating Investigator is responsible for submitting the IND Safety Report to the Investigator's Institutional Review Board (IRB) as per FDA regulations.



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8.3.7 AE Reporting - Sponsor Contact Information

Todd M. Hockemeyer
Vice President – Regulatory Affairs
Zevacor Molecular
7715 Loma Court
Fishers, Indiana 46038
Phone: (317) 417-2860
Fax: (866) 512-7795

The Investigator will fax the initial AE Report Form to the Sponsor as required above.

8.4 Patient Monitoring

Patient subjects will be monitored throughout the imaging process during the administration of the imaging agents and immediately thereafter. Patient subjects will be instructed to inform the study physician and/or study coordinator of any AEs that may occur at any time during the study after the injection of the imaging agents. Patients will be contacted within 24 hours after the investigational scan to assess any AEs/SAEs. They will also be contacted again when imaging report is finalized and sent to their treating physician.

8.5 Investigator Responsibility

The Investigator at the clinical center will completely and promptly record each adverse reaction. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms.

Unless directed otherwise per responsibilities outlined elsewhere in this document, the Investigator is required to report all adverse events to the Sponsor within 30 days of determination of the AE.

8.6 Follow Up

All unresolved AEs, Suspected Adverse Reactions and/or Severe AEs, will be followed by the responsible Investigator until resolved, the patient is stabilized, or the patient is lost to follow-up.



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9.0 STUDY PATIENTS

9.1 Use in Specific Populations, General

This Phase III clinical study will include only men who have a confirmed diagnosis of prostate cancer.

9.1 Women

Choline C11 Injection is not indicated for use in women. Furthermore, there are no adequate and well controlled studies with Choline C11 Injection in pregnant women and the fetal radiation dose from a ¹¹C-choline PET imaging study is unknown. All radiopharmaceuticals, including Choline C11 Injection, have the potential to cause fetal harm. For the purposes of this clinical study allowing for expanded access to this diagnostic agent, female patients and/or pregnant women will not be allowed to participate.

9.2 Pediatric Use

The safety and effectiveness of Choline C11 Injection have not been established in pediatric patients. For the purposes of this clinical study allowing for expanded access to this diagnostic agent, pediatric patients and/or patients under the age of 18 will not be allowed to participate.

10. STUDY ADMINISTRATION

10.1 Quality Assurance / Quality Control

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to study start, and periodic monitoring visits by the Sponsor (or designee). Case report forms will be reviewed for accuracy and completeness by the Sponsor during on-site monitoring visits, and any discrepancies will be resolved with the Investigator or designees, as appropriate. The data will be entered into the clinical trial database and verified for accuracy.

10.1.1 Direct Access To Source Data And Documents

Each Investigator participating in the study will permit trial-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data and documents. All data recorded during the study will be made available by the site for audit against source data and for all compliance with GCP and specific protocol requirements.



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10.1.2 Study Monitoring

All aspects of the study will be monitored by the Sponsor's representative, which will use current GCPs and Standard Operating Procedures (SOPs) for compliance with applicable government regulations. During the conduct of the study, and thereafter until the final report has been completed, the Sponsor's representative will visit each study site at regular intervals by prior arrangement with the Investigator. In order to validate the data in the CRF, the Sponsor's representative will be allowed direct access to the patients' individual source medical records and the study master file. The purpose of these visits is to discuss study progress; verify adherence to the protocol and the completeness, consistency and accuracy of the data entered into the CRFs (source data validation); resolve outstanding data discrepancies; and check on various aspects of the study progress (eg, radiopharmaceutical accountability, sample storage). These individuals must have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator. Each Investigator is to cooperate in this endeavor and ensure that any problems and issues discovered during the course of these monitoring visits are resolved.

10.1.3 Audit and Inspection

All data recorded during the study will be made available by the site for audit against source data and for all compliance with GCP and specific protocol requirements.

A database audit will be performed on the image readings and safety data to detect systematic and random errors. Any errors should be corrected, and, if the error rate is greater than 1 error per 100 fields (1%), a systematic database review should be conducted and corrections made to achieve an error rate of <.5%.

10.1.4 Confidentiality of Patient Data

All information provided to each Investigator by the Sponsor, including preclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be relayed in confidence to the IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study, other than to the Sponsor, the Sponsor's representative, the government agencies, or to the IRB, except as required by law. All data collection and data management will be in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations for (US sites).

The assignment of numbers for patients' identification is based on the desire for anonymity. Patients will be numbered in a manner specified by the Sponsor's representative. Patients will be identified to Sponsor representatives only by their assigned number, initials, and data of birth. Each



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Investigator, however, must maintain a list of all patient names and the above indicated identifying information for each patient that participates in the study at the Investigator's center.

10.2 Data Handling and Record Keeping

10.2.1 Case Report Forms

Adequate and accurate CRFs should be maintained and all relevant observations and data related to the study should be recorded. This should include patient demographic data such as age, race, and gender; medical history and physical examination; a checklist of inclusion and exclusion criteria; biopsy and/or histology results; clinical assessments from patient medical history; AEs; therapeutic treatments and results; and final interpretation and evaluation of imaging studies completed by the readers. The Monitor will review all CRFs and compare data to that contained in clinic notes and patients' medical records to ensure they match.

The CRF will be signed and dated by the Principal Investigator or designee after his/her review. In addition, source documents will be provided. Each Investigator will be responsible for the timeliness, completeness, and accuracy of the CRFs and will make these forms available for thorough review by the Monitor at each scheduled monitoring visit.

All instances of missing or incorrect data must be given the Investigator's full attention. While it is recognized the certain tests may, on occasion, not be performed either through human error, lack of patient cooperation, or in the interest of good medical practice, these instances should be infrequent. In the event they do become frequent, it is the binding legal responsibility of the Sponsor to consider these a protocol violation and to take appropriate corrective measures.

10.2.2 Study Records Retention

United States Federal Regulations require that following completion of a clinical study, a copy of all records pertaining to that study must be maintained by the investigational center for one of the following two time periods:

- At least 2 years after the last approval of a marketing application in the ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region
- At least 2 years after the investigation is discontinued and the FDA has been notified – in situations where no application is filed or if the application is not approved for such indication



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The site will maintain a Clinical Study Document Binder, which will be maintained at the study site. In this binder, there will be tabbed sections for study documents including the following:

- FDA Form 1572
- study personnel identification and signature list
- study staff curricula vitae
- patient screening records
- patient roster identification numbers
- IRB documentation
- all approved versions of protocol and amendments or administrative changes
- all approved versions of ICF
- drug accountability records
- correspondence and site monitoring reports
- blank Case Review Forms (CRFs).

The site must keep the binder current and available for review by the Sponsor, IRB, and/or FDA.

10.3 Termination of the Study

The Sponsor and the Investigator reserve the right to discontinue this study at any time. If this should be necessary, the procedures will be arranged after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the interests of all patients. The Investigator must notify the IRB/EC of study discontinuation, and the Sponsor or the Investigator must supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements. Otherwise, the study is considered terminated upon completion of all patient protocol-scheduled treatments and evaluations.

10.4 Study Report and Publications

Investigators in this study may communicate, orally present, or publish results from this clinical study in scientific journals or other scholarly venues if:

- The overall results of the study have been publicly disclosed in an abstract, manuscript, or presentation form, or with the consent of the Sponsor
- No confidential information will be contained in the presentation or publication

The Investigator will submit any proposed publication or presentation to the Sponsor for review and comment at least 30 days prior to submission.



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11. DRUG SUPPLY

11.1 Drug Production and Compounding

Zevacor Molecular (Zevacor) will be responsible for the production of the ^{11}C -choline PET imaging drug product for use by imaging centers participating in the study. Zevacor will ensure that the PET imaging drug is manufactured according to current Good Manufacturing Practices (cGMP) and is suitable for human use. Zevacor currently produces three PET imaging drug products approved for patient use under 21 CFR 212: Fludeoxyglucose F18 Injection, USP; Sodium Fluoride F18 Injection, USP; and Ammonia N13 Injection, USP. Zevacor's PET drug production facility co-located at the Decatur Memorial Hospital was subject to a complete 6 system inspection by the FDA in October, 2012, and received a positive report with no citations or warnings. Since June 12, 2012, Zevacor Molecular has produced several hundred batches of these PET drug products representing several thousand doses. Each batch was 100% quality control tested for safety and effectiveness as per the compendium for each drug product under the U.S. Pharmacopeia (USP) and National Formulary (NF), published dually as USP-NF. During that time, Zevacor has produced every batch with 100% passing quality and has experienced no customer complaints or product recalls.

Upon commencement of this clinical study, Zevacor will have already submitted an ANDA submission for Choline C11 Injection. This submission is being reviewed under ANDA 206319. The facility, facility operators, and drug product will have been fully qualified according to cGMP and in accordance with the Reference Listed Drug currently manufactured by the Mayo Clinic, Rochester, MN. The Chemistry Manufacturing and Controls (CMC) section of the ANDA, which is used to describe the chemistry, production methods, quality control protocols, adherence to cGMPs, and all qualifying data for the facility, operators, and product batches, is also provided within the IND application to the FDA.

11.2 Packaging and Labeling

Choline C11 Injection is packaged in a multi-dose glass vial (Final Product Container) containing between 148 MBq to 1225 MBq (4mCi to 33mCi) per milliliter of [^{11}C] Choline at EOS calibration time in aqueous 0.9% sodium chloride solution (approximately 10 mL volume).

The product label will contain the information as required by the FDA under 21 CFR 212, the Code of Federal Regulations relevant to PET drug production. The dose will be dispensed and packaged from the Final Product Container by authorized nuclear pharmacists according to correct compounding procedures as defined in the U.S. Pharmacopeia, Chapter 797 and as licensed by the Illinois Board of Pharmacy and the Illinois Emergency Management Agency, Division of Nuclear Safety.



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11.3 Conditions for Storage and Use

Each vial containing Choline C11 Injection will be produced and stored at the Zevacor Molecular drug production facility. The drug product shall be stored at 20 - 25°C; excursions permitted to 15 to 30°C. Choline C11 Injection will be provided in a single dose syringe ready for immediate use. The drug product will expire within 60 minutes of the End of Synthesis (EOS) calibration. Imaging should be initiated immediately after administration of Choline C11 Injection with the acquisition of emission images 0 to 15 minutes from the time of injection.

The drug product will be dispensed according to the patient doctor's prescription under the direction of a Licensed Nuclear Pharmacist. Choline C11 Injection will be aseptically withdrawn and administered from a single dose syringe, containing between 370 MBq – 740MBq or (10 mCi – 20 mCi) in aqueous 0.9% sodium chloride solution. The effective radiation absorbed dose from 740 MBq (20 mCi) dose of Choline C11 Injection is approximately 3.22 mSv (0.32 rem) in an adult.



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Clinical Study Protocol Title Page

Study Title: Expanded Access to ^{11}C choline PET/CT/MR for Staging of Recurrent Prostate Cancer

Test Drug: Choline C11 Injection

Indication Studied: Prostate Cancer Recurrence

Sponsor: Zevacor Molecular

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c. INDEX OF ACRONYMS AND DEFINITIONS

ACR	American College of Radiology
AE	Adverse Effect
ANDA	Abbreviated New Drug Application (FDA submission for approval of generic drugs)
CCI	Cancer Care Institute (Affiliate of Illinois Health & Science)
CFR	Code of Federal Regulations (Legal requirements administered by the FDA)
cGMP	Current Good Manufacturing Practices
CRF	Case Report Forms (Patient study records captured in the study database)
CT	Computed Tomography (Imaging system)
DMH	Decatur Memorial Hospital (Affiliate of Illinois Health & Science)
ECOG	Eastern Cooperative Oncology Group (Cancer rating system)
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
IC	Informed Consent
IND	Investigatory New Drug (Application for a clinical trial of an unapproved drug)
IRB	Institutional Review Board
MR	Magnetic Resonance (Imaging system)
NCCN	National Comprehensive Cancer Network
PET	Positron Emission Tomography (Imaging system)
PSA	Prostate-Specific Antigen (Prostate cancer blood test)
SAE	Severe Adverse Effect
SPECT	Single Photon Emission Computed Tomography (Imaging system)
Tc	Technetium (radioactive isotope used as an imaging drug product)
USP-NF	United States Pharmacopeia – National Formulary



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1. INTRODUCTION

1.4 Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in American men, and the second leading cause of cancer death. Statisticians at the National Cancer Institute estimate that there will be 233,000 new cases of prostate cancer and 29,480 deaths from prostate cancer in 2014 (seer.cancer.gov/statfacts/html/prost.html). Since the prostate specific antigen (PSA) test became commercially available in 1985, most prostate cancers have been discovered through PSA screening. Widespread PSA screening for prostate cancer has resulted in a migration to a lower stage of prostate cancer. For example, rates of lymph node metastasis at diagnosis have declined from 20% in the 1970s and 1980s to less than 4% today. Imaging to detect the presence and location of metastatic prostate cancer has historically relied on the ^{99m}Tc-MDP bone scan and cross-sectional imaging with a CT scan or MRI. In addition to imaging studies, nomograms based on clinical T stage, PSA level, PSA kinetics, Gleason grade, and volume of cancer in biopsy specimens are used to predict the risk of metastasis (Stephenson AJ, Sacrdino, PT, Eastham, JA et al., 2006). More recently, positron emission tomography (PET) using radiopharmaceuticals such as ¹¹C-choline and ¹¹C-acetate has improved detection of metastatic prostate cancer.

1.5 Prostate Cancer Imaging

1.5.1 Relapsed Prostate Cancer

A rising PSA occurs in approximately 20 to 40% of patients within 10 years of definitive treatment of prostate cancer and is known as a biochemical relapse. A biochemical relapse of prostate cancer usually precedes evidence of relapse using conventional imaging. The definition of biochemical relapse after radical prostatectomy is a PSA of 0.2 ng/mL confirmed at that level or a higher level on a subsequent PSA test 3 months later (Cookson MS, Aus G, Burnett AL, et al, 2007). The definition of biochemical relapse after radiation therapy is a PSA level 2 ng/mL above the nadir level after treatment (Roach M, Hanks GE, Thames H, et al, 2006). PSA kinetics, most commonly the PSA doubling time; the initial stage and grade of prostate cancer; and time from treatment to biochemical relapse can be used to predict localized versus metastatic cancer states. However, early identification on imaging studies of relapsed prostate cancer is essential in treatment planning. Results of studies using ¹¹C-choline PET/CT and ¹¹C-acetate PET/CT have shown high sensitivity and specificity at low PSA levels in men with biochemical relapse after primary treatment for prostate cancer.

Two early studies have shown that ¹¹C-acetate PET is more sensitive than ¹⁸F-FDG PET in detection of relapsed prostate cancer (Oyama N, Akino H, Kanamaru H, et al, 2002; Fricke E, Machtens S, Hofmann M, et al, 2003). In a study ¹¹C-choline PET/CT in 41 patients with biochemical relapse after radical prostatectomy sensitivity was 89% with PSA levels < 2.5 ng/mL (Rinnab L, Simon J, Hautmann



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RE, et al, 2009). In a larger study of 190 patients with biochemical relapse after radical prostatectomy, ^{11}C -choline PET/CT detection of prostate cancer was correlated with the PSA level (known as the trigger PSA) and with PSA kinetics. Trigger PSA levels were significantly different between PET-positive and PET-negative patients ($P=0.0001$), and ROC analysis showed an optimal trigger PSA cutoff value of 2.43 ng/mL. Using multivariable analysis, trigger PSA and PSA velocity were independent prediction factors for a positive PET, whereas PSA doubling time was an independent factor for a positive PET scan only in patients with a trigger PSA < 2.0 ng/mL. An important finding of this study was that Gleason grade, pathologic tumor stage and lymph node status, and time from radical prostatectomy to biochemical relapse were not independent prediction factors for a positive PET (Castellucci, P, Fuccio C, Nanni C, et al, 2009).

In a retrospective review reported by the Mayo Clinic, 176 patients with biochemical relapse of prostate cancer after primary treatment underwent ^{11}C -choline PET/CT imaging. Lesions were identified in 32% of the patients by ^{11}C -choline PET/CT which were not detected by conventional imaging. Investigators reported an optimal trigger PSA level 2.0 ng/mL. In this study, a true positive scan was confirmed by pathology of targeted biopsies or of surgical specimens (41.4%), or by conventional imaging. Performance characteristics were sensitivity 93%, specificity 76%, positive predictive value 91% and negative predictive value 81%. This study was limited by the retrospective nature of the data collection and the investigators recognized that prospective studies are needed to compare ^{11}C -choline PET to conventional imaging with bone scan, CT and pelvic MRI (Mitchell, C, Lowe V, Rangel L, et al, 2013).

The choline analog tracer ^{18}F -FCH has been studied in patients with biochemical relapse of prostate cancer with less favorable results than ^{11}C -choline. In a study of 100 patients with biochemical relapse, 89% of patients with trigger PSA < 4 ng/mL were PET negative (Cimitan M, Bortolus R, Morassut S, et al, 2006). In a subsequent study using ^{18}F -FCH in 56 patients with biochemical relapse after radical prostatectomy, sensitivity was 44% when the trigger PSA ranged from 1 to 4 ng/mL (Pelosi E, Arena V, Skanjeti A, et al, 2008).

As ^{11}C -choline has emerged as a favorable diagnostic agent in patients with prostate cancer relapse, studies have been initiated to determine the best imaging modality. ^{11}C -choline PET/CT was compared with ^{11}C -choline PET/MRI in 31 with biochemical relapse. The detection rate for localized relapse was higher and more conclusive for PET/MR which detected 17 regions in 12 patients compared to PET/CT which detected 12 regions in 8 patients. Similar improvements of using MR were also found in detection of lymph node metastases and bone metastases (Eiber M., Souvatzoglou M., Maurer T., et al, 2013).

1.6 Rationale for Study



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Studies of molecular imaging in patients with prostate cancer have shown the following:

5. ^{11}C -choline, ^{18}F -fluorocholine (^{18}F -FCH), and ^{11}C -acetate have shown greater accuracy in prostate cancer staging than conventional imaging or ^{18}F -FDG PET.
6. ^{11}C -choline PET and whole body MRI are complementary, and when combined have the highest sensitivity and specificity in detection of prostate cancer metastasis.
7. ^{11}C -choline has the highest sensitivity at low PSA levels for detection of prostate cancer in men who have a biochemical relapse after primary treatment.
8. ^{11}C -choline PET/CT and PET/MRI are complementary and show the highest sensitivity and specificity in detection of lymph node metastasis when combined.

In patients with biochemical relapse of prostate cancer after primary treatment, early localization of cancer with molecular imaging using ^{11}C -choline PET/CT or PET/MRI can lead to improved treatment planning with observation, local-regional therapy, or with systemic therapy. Molecular imaging using PET drug products and PET imaging techniques have the potential to change the paradigm for treating men with biochemical relapse after radical prostatectomy. In a study of 72 men with biochemical relapse and ^{11}C -choline PET/CT positive lymph node metastasis, salvage lymphadenectomy resulted in a 5-year relapse-free survival of 35% and cancer-specific survival of 75% (Rigatti P, Suardi N, Briganti, A, et al, 2011). Response to treatment can be monitored with PET molecular imaging as well as with PSA, which may lead to earlier additional therapy.

In March 2013, the FDA approved the New Drug Application (NDA) of the Mayo Clinic in Rochester, MN, for the use of ^{11}C -choline as a radiopharmaceutical agent for PET imaging of patients with suspected prostate cancer relapse. ^{11}C -choline has a half-life of 20 minutes, which limits the distribution of the product to Rochester, MN, and the surrounding area. As a result, this diagnostic agent and its associated benefits have limited availability to patients.

The key objective of this study is to provide expanded access to this drug product as currently defined under the reference listed drug label as an investigational drug in geographical service areas where ^{11}C -choline is not available.

2. STUDY OBJECTIVES

Based on these rationales, this protocol within this clinical trial will address the following objective:

- F. Provide expanded access to the drug ^{11}C -choline.



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3. ETHICS

3.1 Institutional Review Board

An Investigational Review Board (IRB) will assess and approve the Investigatory New Drug (IND) application. This will include approval of the IND Protocol, Investigator's Brochure, and the Informed Consent. The Principal Investigator and Sponsor will provide the IRB with appropriate reports on the progress of the study, including safety updates, in accordance with applicable FDA regulations and in agreement with policy defined by sponsor and as outlined in this protocol. All amendments to the study will be sent to the IRB for information (minor amendment) or for approval (major amendment) before implementation of the study amendments.

Decatur Memorial Hospital (DMH) and the Cancer Care Institute (CCI, an affiliate of DMH) are both located in Decatur, Illinois. The Decatur Memorial Hospital Institutional Review Board (DMH IRB) will be involved in all aspects of study planning and considerations as per 21 CFR part 56. The DMH IRB is covered under Decatur Memorial Hospital's Federal Wide Assurance (FWA) # of 00006097. The DMH IRB reviews research projects which involve human participants to ensure that two broad standards are upheld: first, that participants are not placed at undue risk; second, that they give un-coerced, informed consent to their participation.

3.2 Ethical Conduct of Study

The study shall be performed in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations, Food and Drug Administration (FDA) Good Clinical Practice (GCP) regulations as defined within the Code of Federal Regulations, 21 CFR parts 50, 56, and 312 and clinical safety data management (E2A) regulations. The Principal Investigator / Sponsor shall provide the IRB with all relevant material, including copies of the IND protocol, Informed Consent, Investigator's Brochure and any subject information or advertising materials. The study shall not be initiated until the IRB provides written approval of the protocol and the informed consent.

Each study subject shall be required to provide written authorization that their patient information can be disclosed and used by the Principal Investigator and other researchers as well as the Sponsor for the purposes of assessing the efficacy of the study drug and imaging protocol.

3.3 Patient Information and Informed Consent

In compliance with the requirements set forth by the FDA in 21 CFR Part 50, a properly written and executed Informed Consent shall be obtained from each study subject prior to enrollment and initial screening evaluations required by this protocol. The IC has been reviewed by the Sponsor for acceptability and shall be presented by the Principal Investigator, together with the IND protocol and



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Investigator's Brochure, to the IRB for review and approval prior to the start of the study. The IC shall be written in such a way as to be fully comprehensible by the prospective study participant.

The Informed Consent shall be revised in the event new information becomes available during the study that may be relevant to the subject. Any revision shall be submitted to the IRB for review and approval before use.

It is the Principal Investigator's responsibility to obtain a properly written and executed Informed Consent from the study subject only after there has been an adequate explanation of the goals, methods, anticipated benefits and potential hazards of the study. The subject shall be given ample time to inquire about details of the study and decide whether to participate in the study. The IRB-approved IC shall be signed and dated by the subject and by the person conducting the informed consent discussion. A copy of the properly executed IC shall be provided to the study subject. The original signed informed consent shall be kept in a confidential location on site.

4. STUDY PATIENTS

4.1 Patient Study Population

Decatur Memorial Hospital (DMH), a not-for-profit division of Illinois Health & Science, will be the site designated for imaging the study subjects and evaluating the ^{11}C -choline PET/CT and PET/MR imaging data. Patients will be referred from within the institution as well as from outside treatment organizations. Urology, radiation oncology and medical oncology practices within an approximately 300 mile radius of the DMH imaging center will be contacted for enrollment of patients into this study. As such, this study will encompass patients being served in major cities, such as Chicago, St. Louis, Cincinnati, Louisville and Indianapolis who would otherwise have to seek ^{11}C -choline PET imaging at the Mayo Clinic in Rochester, MN. In the event that patients outside of the recruitment area wish to enroll in the clinical trial, they will also be considered. A primary source for patients will also be from The Cancer Care Institute, also a not-for-profit division of Illinois Health & Science. This phase III study is planned to provide expanded access to as many patients who elect to participate in the study that are over the age 18 and have experienced a biochemical relapse of prostate cancer after primary treatment.

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria:

2. Suspected prostate cancer recurrence based upon elevated blood prostate specific antigen (PSA) levels following initial therapy.



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3. Non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging.

4.1.2 Exclusion Criteria

None.

4.2 Subject Withdrawal And Replacement

4.2.1 Criteria For Subject Withdrawal

Subject participation may be withdrawn / discontinued for the following reasons (but not limited to):

4. Patient request for any reason to discontinue participation within the clinical trial.
5. Patient non-compliance with the accepted protocol.
6. Suspension or discontinuation of the clinical trial by the Sponsor, Zevacor Molecular.

4.2.2 Procedures for Subject Withdrawal

Study patients who decide to discontinue the protocol and withdraw from the clinical trial will be seen and assessed by an Investigator. The reason(s) for the withdrawal and the date of the withdrawal will be documented in the study records for the patient.

If death is the reason for the withdrawal from the clinical trial, there are two options for categorizing as such: 1) progressive disease, or 2) a Serious Adverse Event (SAE). Although more than one SAE may be documented as reason for withdrawal, only one SAE will be documented as the cause of death.

At withdrawal, all on-going study-related AEs and SAEs must be followed until resolution, unless in the Investigator's opinion the condition is unlikely to be resolved due to the patient's underlying disease.

5. INVESTIGATIONAL PLAN

5.2 Expanded Access Study Protocol: Emergent Use

The study will consist of patients who have a biochemical relapse or other evidence of relapse after primary treatment. This study group of patients who, upon suspected recurrence, have subsequently experienced non-informative bone scintigraphy, computerized tomography (CR) or magnetic resonance imaging.

7. Informed consent will be obtained from all participants before any study related procedures are conducted. Each participant will be informed about the nature of the study, its purpose, and possible risks. Informed consent will be documented by using the written informed consent document approved by the local IRB at the Decatur Memorial Hospital.
8. At the time of referral, patients will be asked to bring their prior records as it pertains to their prostate cancer history. Data collected from outside records, such as radiographic studies, previous imaging studies and biopsies will be incorporated into the study record. Current data will be collected to support eligibility only; no historical data or future data will be collected.
9. Abstracted data for the study record will include:
 - a. Pathology reports
 - b. Imaging reports
 - c. Date(s) of biochemical relapse and coordinating PSA resultsOnce all records have been assessed for eligibility, an order for the ^{11}C -choline PET CT scan and MRI scan will be requested from the referring physician and patient will be scheduled and given the appropriate prep instructions.
10. Patients entered into the study will undergo a ^{11}C -choline PET CT scan and/or MRI scan. The CT scan will be performed with intravenous contrast unless deemed unsafe by lab values. The CT and MRI images will be evaluated for evidence of metastatic prostate cancer. The ^{11}C -choline PET CT and MRI images will be evaluated for evidence of metastatic prostate cancer.
11. Upon conclusion of each imaging protocol, the referring physician will receive written documentation of the results. At this time, the patient will be considered off study and no further follow up is required.

5.2 Imaging Protocols - ^{11}C Choline PET/CT/MRI

3. ^{11}C choline PET/CT Imaging Protocol:
 - Patient should hydrate with 16 ounces of water prior to the imaging study
 - Fasting is required for at least 6 hours
 - Void prior to study
 - 15 - 20 mCi ^{11}C -choline IV Injection
 - 5 min delay after injection.
 - PET images skull base to mid thigh with 3 min per bed position
 - Image acquisition order changed due to bladder filling
 - If CT before MRI, then images obtained top to bottom
 - If MRI before CT, then images obtained bottom to top



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- CT skull base to mid thigh for attenuation correction
 - Use of IV contrast, if applicable, based on ACR IV contrast guidelines renal function screening protocol
 - Slice thickness 2.5, kvp 120, mA 100, exposure time 500, 80 - 100 cc contrast
 - Fusion of PET and CT images
4. MRI whole body imaging protocol:
- No IV contrast
 - High resolution axial T2 prostate bed, axial DWI pelvis, coronal T2 skull base to mid thighs
 - Fusion of coronal and PET images

5.3 Imaging Technology

The imaging studies referenced above will be conducted as defined in Section 5.2 above. The CT and MR studies must be performed as one continuous procedure using the GE Trimodality PET Imaging System. This will require the patient to be immobile for approximately 60 minutes as each imaging study is executed.

The GE Trimodality PET Imaging System consists of the following integrated equipment: GE Discovery PET/CT 7.0 Imaging System, a GE Discovery MR750w 3.0T Imaging System, and the Lateral Docking Trimodality Patient Transporter. This system will allow for the combined imaging of PET, CT, and MR modalities in one integrated session using the Lateral Docking Transporter to ensure image synchronization between the modalities.

5.4 Imaging Review and Interpretations

5.4.1 Image Review

For this Expanded Access protocol, there will not be any study related interpretation or use of any imaging.

5.4.3 Image Assessment Criteria

NONE

5.5 Study Data – Statistical Analysis

- Sample Size:



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This study has been established to provide expanded access to the radioactive diagnostic imaging agent Choline C11 Injection in conjunction with PET/CT and/or MRI scans.

It is anticipated that during this study at least 100 patients maybe admitted into the study under expanded access. In the event that more than 100 patients request to be permitted into the expanded access study, Zevacor Molecular, the study sponsor, will formally petition the FDA to increase the study population.

- **Data Analysis:**

This protocol is to provide expanded access only. The patient data obtained for this protocol will not be further analyzed beyond that need for clinical diagnosis.

5.6 Publishing the Study Data

Study data for this expanded access protocol will not be published.

6.0 CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

6.1 Contraindications

None

6.2 Warnings and Precautions

- Imaging errors have been reported during previous clinical studies with ¹¹C-choline PET and PET/CT imaging. A negative image does not rule out the presence of recurrent prostate cancer and a positive image does not confirm the presence of recurrent cancer. ¹¹C-choline uptake is not specific for prostate cancer and may occur with other types of cancer, such as lung carcinoma and brain tumors.
- Blood PSA levels < 2 ng/mL have been associated with poor performance ¹¹C-choline PET imaging, with indications of higher numbers of false positive and false negative results.
- Tissue inflammation as well as prostatic hyperplasia have been associated with false positive ¹¹C-choline PET images.



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- Concomitant colchicine or androgen-deprivation therapeutic drugs, such as luteinizing hormone-releasing analogs and anti-androgen drugs, may interfere with ^{11}C -choline PET imaging. One published report of ^{18}F methylcholine PET imaging indicated that discontinuation of colchicine for two weeks resolved the colchicine effect. The impact of discontinuation of androgen-deprivations therapy upon ^{11}C -choline PET imaging has not been established.

6.3 Limitation of Use

^{11}C -choline PET imaging is NOT a replacement for histologic verification of relapsed prostate cancer.

7. ASSESSMENT OF SAFETY

7.1 Radiation Safety – Drug Handling

^{11}C -choline is a radioactive drug and will be handled with appropriate safety measures to minimize radiation exposure during administration. The use of waterproof gloves and effective shielding when handling ^{11}C -choline will be required. Radiopharmaceuticals, such as ^{11}C -choline will only be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radioactive materials, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

^{11}C -choline will be delivered to a Certified Nuclear Medicine Technician (CNMT) or equivalently qualified personnel in individual, single dose syringes contained within a NRC/DOT approved syringe shield specifically designed for minimizing radiation exposure during handling. The safe handling of Radioactive Material will be as defined within the Sponsors' radioactive material license issued by the Illinois Energy Management Agency (IEMA), the state nuclear regulatory agency responsible for radioactive material within the State of Illinois.

7.2 Radiation Risks – Patients

^{11}C -choline contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Safe handling should be ensured to minimize radiation exposure to the patient.

7.3 Indications and Usage

^{11}C -choline is a radioactive diagnostic agent initially approved for use by the U.S. Food & Drug Administration in 2012 for positron emission tomography (PET) imaging of patients with suspected prostate cancer relapse and non-informative bone scintigraphy computed tomography. It is dispensed



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and administered under the reference listed drug (RLD) label: 233155. For the purposes of this study, ^{11}C -choline will be produced, dispensed and administered according to the prescribing information as detailed in the approved drug labeling.

7.4 Patient Safety Evaluations

Patient safety will be evaluated prior to participation in the study and before execution of each of the imaging protocols by screening process.

7.5 Safety Review

An Institutional Review Board (IRB) will review the protocol of this study for safety and effectiveness prior to its implementation. The IRB will convene to approve the Clinical Protocol as defined in this document as well as the Informed Consent, as defined in the U.S. Code of Federal Regulations, 21 CFR 50 and 56. The IRB will also meet on an as needed basis to examine any potential safety issues and the overall conduct of the trial.

8.0 ADVERSE REACTIONS

8.1 Adverse Reactions, General

Exclusive of an uncommon, mild injection site reaction, no adverse reactions to ^{11}C -choline have been reported.

8.2 Allergic Reactions

As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel will be immediately available during and within a reasonable time soon after the imaging procedures defined in the clinical protocol.

8.3 IND Safety Reporting Requirements

8.3.1 21 CFR 312

The U.S. Code of Federal Regulations, section 21 CFR 312, defines the conditions within which Adverse Events (AE) and Severe Adverse Events (SAE) are reported to the FDA. For the purposes of this study, the sponsor will be responsible for reporting AEs and SAEs to the FDA as defined by these regulations.

8.3.2 Adverse Events



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Adverse Event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event, also referred to as an adverse experience, can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality.

An adverse event may be any of the following:

5. A new illness
6. An exacerbation or a sign or symptom of the underlying condition under treatment or of a concomitant illness
7. Unrelated to participation in the clinical study or an effect of the study radiopharmaceutical or comparator drug
8. A combination of 1 or more of the above factors

An exacerbation of a pre-existing condition/illness is defined as a more frequent occurrence or as an increase in the severity of the pre-existing condition/illness during the study. Planned or elective surgical procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during planned or elective surgery is an AE. Conditions leading to unplanned surgical procedures may be AEs.

The period of observation for collection of (treatment-emergent) AEs extends from the time the subject takes the first dose of study radiopharmaceutical until their exit from the study. The patient will be called within 24 hours after the protocol scan to assess any AEs and SAEs.

In the event of an adverse event, the Investigator is required to file an Adverse Event Report using the AE Report Form to the sponsor within a reasonable period of time, but no later than 3 days after the event has been recognized by the Investigator. The Sponsor contact information for reporting AEs is listed in section 8.3.7 below.

8.3.3 Suspected Adverse Reactions

Suspected Adverse Reaction means 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' means 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 adverse reaction, which means any adverse event caused by a drug.



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It is the responsibility of the Sponsor to determine whether the Adverse Event should be classified as a Suspected Adverse Reaction.

8.3.4 Serious Adverse Events (SAEs)

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
- a 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 functions
- a congenital anomaly/birth defect

Important medical events that may not result in death, be 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.

In the event of an SAE, the Investigator is required to file an Adverse Event Report using the AE Report Form to the sponsor within 24 hours of the Investigator’s recognition of the SAE. The Sponsor contact information for reporting AEs is listed in section 8.3.7 below.

8.3.5 Unexpected Adverse Events

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "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.



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8.3.6 Submission of IND Safety Reports

The sponsor must report in an IND safety report any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the sponsor needs to ensure that the event meets all three of the definitions:

- Suspected adverse reaction
- Serious
- Unexpected

If the Sponsor concludes that there is a significant likelihood that the imaging drug caused the adverse event, an IND Safety Report will be submitted to the FDA. In the event that the AE is found to be unexpected, fatal, or life-threatening, the sponsor is required to notify FDA and all participating investigators by fax or phone within 7 calendar days of the initial receipt of information. A written IND safety report must follow within 15 calendar days. All other AEs that are found to be causal to the imaging agent and are unexpected must be submitted in writing within 15 calendar days.

Each participating Investigator is responsible for submitting the IND Safety Report to the Investigator's Institutional Review Board (IRB) as per FDA regulations.

8.3.7 AE Reporting - Sponsor Contact Information

Todd M. Hockemeyer
Vice President – Regulatory Affairs
Zevacor Molecular
7715 Loma Court
Fishers, Indiana 46038
Phone: (317) 417-2860
Fax: (866) 512-7795

The Investigator will fax the initial AE Report Form to the Sponsor as required above.

8.4 Patient Monitoring

Patient subjects will be monitored throughout the imaging process during the administration of the imaging agents and immediately thereafter. Patient subjects will be instructed to inform the study physician and/or study coordinator of any AEs that may occur at any time during the study after the injection of the imaging agents. Patients will be contacted within 24 hours after the investigational scan



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to assess any AEs/SAEs. They will also be contacted again when imaging report is finalized and sent to their treating physician.

8.5 Investigator Responsibility

The Investigator at the clinical center will completely and promptly record each adverse reaction. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms.

Unless directed otherwise per responsibilities outlined elsewhere in this document, the Investigator is required to report all adverse events to the Sponsor within 30 days of determination of the AE.

8.6 Follow Up

All unresolved AEs, Suspected Adverse Reactions and/or Severe AEs, will be followed by the responsible Investigator until resolved, the patient is stabilized, or the patient is lost to follow-up.

9.0 STUDY PATIENTS

9.1 Use in Specific Populations, General

This expanded access protocol of this Phase III clinical study will include only men who have a confirmed diagnosis of prostate cancer.

9.1 Women

Choline C11 Injection is not indicated for use in women. Furthermore, there are no adequate and well controlled studies with Choline C11 Injection in pregnant women and the fetal radiation dose from a ¹¹C-choline PET imaging study is unknown. All radiopharmaceuticals, including Choline C11 Injection, have the potential to cause fetal harm. For the purposes of this clinical study allowing for expanded access to this diagnostic agent, female patients and/or pregnant women will not be allowed to participate.

9.2 Pediatric Use

The safety and effectiveness of Choline C11 Injection have not been established in pediatric patients. For the purposes of this clinical study allowing for expanded access to this diagnostic agent, pediatric patients and/or patients under the age of 18 will not be allowed to participate.



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10. STUDY ADMINISTRATION

10.1 Quality Assurance / Quality Control

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to study start, and periodic monitoring visits by the Sponsor (or designee). Case report forms will be reviewed for accuracy and completeness by the Sponsor during on-site monitoring visits, and any discrepancies will be resolved with the Investigator or designees, as appropriate. The data will be entered into the clinical trial database and verified for accuracy.

10.1.1 Direct Access To Source Data And Documents

Each Investigator participating in the study will permit trial-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data and documents. All data recorded during the study will be made available by the site for audit against source data and for all compliance with GCP and specific protocol requirements.

10.1.2 Study Monitoring

All aspects of the study will be monitored by the Sponsor's representative, which will use current GCPs and Standard Operating Procedures (SOPs) for compliance with applicable government regulations. During the conduct of the study, and thereafter until the final report has been completed, the Sponsor's representative will visit each study site at regular intervals by prior arrangement with the Investigator. In order to validate the data in the CRF, the Sponsor's representative will be allowed direct access to the patients' individual source medical records and the study master file. The purpose of these visits is to discuss study progress; verify adherence to the protocol and the completeness, consistency and accuracy of the data entered into the CRFs (source data validation); resolve outstanding data discrepancies; and check on various aspects of the study progress (eg, radiopharmaceutical accountability, sample storage). These individuals must have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator. Each Investigator is to cooperate in this endeavor and ensure that any problems and issues discovered during the course of these monitoring visits are resolved.

10.1.3 Audit and Inspection

All data recorded during the study will be made available by the site for audit against source data and for all compliance with GCP and specific protocol requirements.



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A database audit will be performed on the image readings and safety data to detect systematic and random errors. Any errors should be corrected, and, if the error rate is greater than 1 error per 100 fields (1%), a systematic database review should be conducted and corrections made to achieve an error rate of <.5%.

10.1.4 Confidentiality of Patient Data

All information provided to each Investigator by the Sponsor, including preclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be relayed in confidence to the IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study, other than to the Sponsor, the Sponsor's representative, the government agencies, or to the IRB, except as required by law. All data collection and data management will be in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations for (US sites).

The assignment of numbers for patients' identification is based on the desire for anonymity. Patients will be numbered in a manner specified by the Sponsor's representative. Patients will be identified to Sponsor representatives only by their assigned number, initials, and data of birth. Each Investigator, however, must maintain a list of all patient names and the above indicated identifying information for each patient that participates in the study at the Investigator's center.

10.2 Data Handling and Record Keeping

10.2.1 Case Report Forms

Adequate and accurate CRFs shall be maintained and all relevant observations and data related to the study shall be recorded. This shall include the patient data needed to determine inclusion into the study.

The CRF will be signed and dated by the Principal Investigator or designee after his/her review. In addition, source documents will be provided. Each Investigator will be responsible for the timeliness, completeness, and accuracy of the CRFs and will make these forms available for thorough review by the Monitor at each scheduled monitoring visit.

All instances of missing or incorrect data must be given the Investigator's full attention. While it is recognized the certain tests may, on occasion, not be performed either through human error, lack of patient cooperation, or in the interest of good medical practice, these instances should be infrequent. In the event they do become frequent, it is the binding legal responsibility of the Sponsor to consider these a protocol violation and to take appropriate corrective measures.

10.2.2 Study Records Retention

United States Federal Regulations require that following completion of a clinical study, a copy of all records pertaining to that study must be maintained by the investigational center for one of the following two time periods:

- At least 2 years after the last approval of a marketing application in the ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region
- At least 2 years after the investigation is discontinued and the FDA has been notified – in situations where no application is filed or if the application is not approved for such indication

The site will maintain a Clinical Study Document Binder, which will be maintained at the study site. In this binder, there will be tabbed sections for study documents including the following:

- FDA Form 1572
- study personnel identification and signature list
- study staff curricula vitae
- patient screening records
- patient roster identification numbers
- IRB documentation
- all approved versions of protocol and amendments or administrative changes
- all approved versions of ICF
- drug accountability records
- correspondence and site monitoring reports
- blank Case Review Forms (CRFs).

The site must keep the binder current and available for review by the Sponsor, IRB, and/or FDA.

10.3 Termination of the Study

The Sponsor and the Investigator reserve the right to discontinue this study at any time. If this should be necessary, the procedures will be arranged after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the interests of all patients. The Investigator must notify the IRB/EC of study discontinuation, and the Sponsor or the Investigator must supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements. Otherwise, the study is considered terminated upon completion of all patient protocol-scheduled treatments and evaluations.



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10.4 Study Report and Publications

Study data will not be published. However, any reporting requirements as defined by 21 CFR 310.33, Annual Reporting, shall be submitted directly to the FDA.

11. DRUG SUPPLY

11.1 Drug Production and Compounding

Zevacor Molecular (Zevacor) will be responsible for the production of the ¹¹C-choline PET imaging drug product for use by imaging centers participating in the study. Zevacor will ensure that the PET imaging drug is manufactured according to current Good Manufacturing Practices (cGMP) and is suitable for human use. Zevacor currently produces three PET imaging drug products approved for patient use under 21 CFR 212: Fludeoxyglucose F18 Injection, USP; Sodium Fluoride F18 Injection, USP; and Ammonia N13 Injection, USP. Zevacor's PET drug production facility co-located at the Decatur Memorial Hospital was subject to a complete 6 system inspection by the FDA in October, 2012, and received a positive report with no citations or warnings. Since June 12, 2012, Zevacor Molecular has produced several hundred batches of these PET drug products representing several thousand doses. Each batch was 100% quality control tested for safety and effectiveness as per the compendium for each drug product under the U.S. Pharmacopeia (USP) and National Formulary (NF), published dually as USP-NF. During that time, Zevacor has produced every batch with 100% passing quality and has experienced no customer complaints or product recalls.

Upon commencement of this clinical study, Zevacor will have already submitted an ANDA submission for Choline C11 Injection. This submission is being reviewed under ANDA 206319. The facility, facility operators, and drug product will have been fully qualified according to cGMP and in accordance with the Reference Listed Drug currently manufactured by the Mayo Clinic, Rochester, MN. The Chemistry Manufacturing and Controls (CMC) section of the ANDA, which is used to describe the chemistry, production methods, quality control protocols, adherence to cGMPs, and all qualifying data for the facility, operators, and product batches, is also provided within the IND application to the FDA.

11.2 Packaging and Labeling

Choline C11 Injection is packaged in a multi-dose glass vial (Final Product Container) containing between 148 MBq to 1225 MBq (4mCi to 33mCi) per milliliter of [¹¹C] Choline at EOS calibration time in aqueous 0.9% sodium chloride solution (approximately 10 mL volume).



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The product label will contain the information as required by the FDA under 21 CFR 212, the Code of Federal Regulations relevant to PET drug production. The dose will be dispensed and packaged from the Final Product Container by authorized nuclear pharmacists according to correct compounding procedures as defined in the U.S. Pharmacopeia, Chapter 797 and as licensed by the Illinois Board of Pharmacy and the Illinois Emergency Management Agency, Division of Nuclear Safety.

11.3 Conditions for Storage and Use

Each vial containing Choline C11 Injection will be produced and stored at the Zevacor Molecular drug production facility. The drug product shall be stored at 20 - 25°C; excursions permitted to 15 to 30°C. Choline C11 Injection will be provided in a single dose syringe ready for immediate use. The drug product will expire within 60 minutes of the End of Synthesis (EOS) calibration. Imaging should be initiated immediately after administration of Choline C11 Injection with the acquisition of emission images 0 to 15 minutes from the time of injection.

The drug product will be dispensed according to the patient doctor's prescription under the direction of a Licensed Nuclear Pharmacist. Choline C11 Injection will be aseptically withdrawn and administered from a single dose syringe, containing between 370 MBq – 740MBq or (10 mCi – 20 mCi) in aqueous 0.9% sodium chloride solution. The effective radiation absorbed dose from 740 MBq (20 mCi) dose of Choline C11 Injection is approximately 3.22 mSv (0.32 rem) in an adult.



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