2017-144 Monitoring Telotristat Ethyl Inhibition of Tryptophan hydroxylase (TPH) in Neuroendocrine Tumors Using α-[^{11}C]methyl-L-tryptophan (AMT)-PET
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Principal Investigator: Anthony F. Shields, MD, PhD
Tel: 313-576-8735; Fax: 313-576-8767
Email: shieldsa@karmanos.org
4100 John R Street, HW04HO
Detroit, MI, 48201

Co- Investigator: Csaba Juhasz, MD, PhD
Philip A. Philip, MD, PhD
Mohammed Al Hallak, MD
Lynette M. Guziatek-Trojniak, RN, MSN, CNP
Wei Chen, PhD - Biostatistician

PROTOCOL SUMMARY

OBJECTIVES:
Primary objective is to show that telotristat ethyl (Xermelo™), a recently FDA-approved TPH inhibitor drug, will decrease tumoral AMT uptake and trapping as compared to values measured at baseline before the start of treatment. Secondary objective is to show that neuroendocrine tumors (NETs) will have increased AMT uptake on positron emission tomography (PET), as compared to surrounding non-tumor tissue at baseline.

PATIENT POPULATION:

1. Histopathologically confirmed, well-differentiated metastatic NETs.
2. Patients receiving stable-dose somatostatin analogs (SSAs, long-acting release [LAR], depot) for > 3 months before enrollment.

STUDY DESIGN:
Imaging will be done with AMT-PET/CT, under separate protocol 2011-053, at baseline and after 9-14 days treatment on telotristat ethyl, 250 mg po three times daily.

EVALUATION:
Prior to PET imaging: Physical exam, CBC and Multiphasic (electrolytes, renal and liver function) drawn within 28 days of start of the study as part of routine care. Radiology testing to measure tumor size (for example, CT scans, MRI scans, PET scans) which are part of routine care. Scan may be done within 8 weeks of the start of the study. A negative urine or blood pregnancy test must be obtained in women with child bearing potential on the day of the first PET scan.

PRIMARY and Secondary ENDPOINTS:
The measurement of the uptake and retention of AMT will be quantitated by maximum standardized uptake values (SUVmax) and compartmental modeling (in tumors with the left ventricle of the heart in the field-of-view) before and after treatment with telotristat ethyl. The proportion of patients whose reduction in AMT uptake between baseline and follow-up is ≥20% will be the primary endpoint. We will also assess if the NET is visible above background at baseline and will also quantify the percent difference in AMT uptake between the tumor mass and background. Using time-activity curves, we will also identify the optimal time frame where tumoral AMT uptake peaks.

STATISTICAL PLAN:
This is a single arm single institution prospective proof-of-concept study. The proportion of patients, who achieved SUVmax reduction of 20% or more, will be estimated and exact (Clopper-Pearson) confidence interval will be calculated. Paired t test will be used for pre- and post- treatment SUVs if normality assumption holds. The relationship of one PET parameter to another will be visualized with scatter plot and measured using linear regression models.

I. OBJECTIVES

1. **Primary Objective:** The primary objective of this pilot study is to evaluate the effect of telotristat ethyl treatment in patients with advanced neuroendocrine tumors (NETs) using α-[^{11}C]methyl-L-tryptophan (AMT)-positron emission tomography (PET) as measured by changes in tumor maximum standardized uptake value (SUVmax).
2. **Secondary Objectives:**
   - **a.** Show that NETs will have increased AMT uptake on PET, as compared to surrounding non-tumor tissue at baseline
   - **b.** Use compartmental modeling (in tumors with the left ventricle of the heart in the field-of-view) to measure change in AMT retention.
   - **c.** Measure change in AMT retention as SUVmean

II. BACKGROUND

AMT-PET to study serotonin synthesis *in vivo*. Alpha-methyl-L-tryptophan (AMT) is an analog of tryptophan, the precursor of the neurotransmitter serotonin (5-HT, 5-hydroxytryptamine). In the early 1990s, Diksic and colleagues at the Montreal Neurological Institute performed extensive animal studies of radiolabeled AMT to validate AMT as a tracer for the measurement of the rate of serotonin synthesis *in vivo* with positron emission tomography (PET) (Diksic et al., 1990, 1991). After the administration of labeled AMT in rats, autoradiograms demonstrated a distribution of high tracer concentration in serotonergic cell bodies in the raphe nuclei. The synthesis of α-methyl-serotonin in brain after tracer administration was confirmed by high performance liquid chromatography (Missala and Sourkes, 1988; Diksic et al., 1990). The [^{3}H] α-methyl-serotonin synthesized in brain was localized to serotonergic neurons and nerve terminals by combined autoradiography and tryptophan hydroxylase (TPH) immunocytochemistry at the electron microscopic level (Cohen et al., 1995). In addition, [^{11}C]AMT, unlike tryptophan, was not incorporated into protein in significant amounts (Madras and Sourkes, 1965; Diksic et al., 1990). These studies demonstrated that [^{11}C]AMT was a suitable tracer for the measurement of serotonin synthesis *in vivo* in humans with PET.

Effect of inhibition of tryptophan hydroxylase (TPH) on AMT trapping. Autoradiographic studies with alpha-[^{14}C]methyl-L-tryptophan in rats have demonstrated that trapping of this radiotracer in the brain was drastically reduced (by 40-80%) following treatment with p-chlorophenylalanine (PCPA), a TPH inhibitor (Tohyama et al., 2002). In contrast, the inhibition of protein synthesis with CXM did not have a significant effect on the global brain trapping of AMT and 5-HT synthesis. In another study, the TPH activation inhibitor AGN-2979 has led to an up to 35% decrease of AMT trapping in the raphe nuclei (Hasegawa et al., 2005). These studies provided proof-of-principle data that measurement of AMT trapping may be useful to assess TPH activity in living tissue.

Imaging epileptic foci and human tumors by AMT-PET. Our group at Wayne State University introduced the use of [^{11}C]AMT-PET for the detection of epileptogenic lesions (Chugani et al., 1998; Juhasz et al., 2003; 2004) and a variety of cerebral and extracerebral tumors (Juhasz et al., 2006; 2009; 2012; 2014;

Bosnyak et al., 2015; 2016; 2017). High AMT transport and trapping was detected in cerebral gliomas, meningiomas as well as lung cancers and breast cancers, with various tumor types showing differences in tryptophan uptake and kinetics. Importantly, increased AMT uptake was commonly detected even in low-grade gliomas and meningiomas (Juhasz et al., 2006; 2011; Alkonyi et al., 2012; Bosnyak et al., 2015). Increased uptake and trapping of AMT in various tumors may have been affected by increased transporter activity as well as increased activity of enzymes converting tryptophan to its metabolites.

Tryptophan PET imaging in carcinoid tumors. Most NETs have an overactive serotonin pathway with increased TPH activity, thus inducing carcinoid syndrome, a condition associated with tumoral secretion of serotonin and clinical symptoms of diarrhea, flushing, bronchial constriction, as well as the development of cardiac valvular fibrosis. Diarrhea is one of the most prominent symptoms of carcinoid syndrome. Imaging TPH activity *in vivo* by PET would be useful to visualize these tumors and evaluate baseline TPH enzyme activity as well as monitor efficacy of TPH inhibitor drugs. Although AMT-PET has not been tested in carcinoid tumors, studies with other amino acid PET radiotracers, including a tryptophan derivative (^{11}C-5-hydroxy-tryptophan) demonstrated high sensitivity to detect carcinoid tumors as small as 5mm in diameter (Koopmans et al., 2008). Highest sensitivities (81-92%) were achieved in lesions located in bone, abdomen/pelvis, liver, head and neck regions. These data make it likely that AMT-PET will be able to detect carcinoid tumors in various locations, and it is reasonable to assume that its uptake and kinetic properties will be modulated by changes in tumoral TPH activity.

Serotonin and cancer proliferation. Many studies have demonstrated that serotonin may a play an important role in tumor growth and vascularity of breast, prostate, and many other tumor types (Siddiqui et al., 2006; Sonier et al., 2006; Dizeyi et al., 2011; Sarrouilhe et al., 2015). At high levels serotonin may promote tumor proliferation, while at lower levels it may even inhibit growth, in part from decreasing tumor blood supply. This is evident in studies using a number of serotonin receptor agonists and antagonists, which have stimulated or inhibited growth depending on the concentration.

Telotristat ethyl is an oral small-molecule TPH inhibitor that has a high molecular weight and acidic moieties, which inhibit it from crossing the blood-brain barrier (Liu et al., 2008; Lapuerta et al., 2015). As the drug has recently become available for clinical treatment of carcinoid-related diarrhea, there is an urgent need to evaluate non-invasive techniques to assess drug effects.

Telotristat ethyl has been shown to inhibit tumor growth in a retrospective study of 200 patients with NET (Morse et al., 2020). After initiation of telotristat ethyl they observed a mean decrease of 0.6 cm in tumor size ($p = 0.006$) and decrease in tumor growth ($p = 0.045$). It will be of interest to determine using AMT-PET if we can measure inhibition of serotonin synthesis and serve as a biomarker in studies assess this activity of this pathway. The use of telotristat ethyl may inhibit tumor proliferation and the image of AMT uptake may provide a predictive marker of this effect. If promising, PET imaging with AMT or an ^{18}F-labeled analog (with a longer half-life) (see, e.g., Michelhaugh et al., 2016; Giglio et al., 2017) could be useful to monitor effectiveness of TPH inhibition in future multicenter studies and clinical trials.

The central hypothesis of this pilot study is that (i) that telotristat ethyl (Xermelo™) (Kulke et al., 2017), a recently FDA-approved TPH inhibitor drug, will decrease tumoral AMT uptake and trapping as compared to values measured at baseline before the start of treatment. (ii) carcinoid tumors will show increased AMT uptake on PET, as compared to surrounding non-tumor tissue at baseline.

As a first step, in this pilot study we will perform AMT-PET imaging in 6 evaluable patients with previously diagnosed mNETs, not previously treated with TPH inhibitor, to characterize the baseline and post-treatment uptake patterns of these tumors and test the feasibility to use AMT-PET for evaluating activity of TPH after inhibitor treatment.

III. PATIENT SELECTION

Inclusion:

1. Eligible patients must be $\geq$ 18 years of age.
2. Histopathologically confirmed, well-differentiated metastatic NETs
3. Receiving stable-dose somatostatin analog (long-acting release [LAR], depot) for > 3 months before enrollment.
4. Patients with 5-HIAA levels above or below the upper limit of normal range and those with unknown values at baseline are allowed to participate.
5. Able to lie within the PET scanner for at least 70 minutes while undergoing scanning.
6. ECOG performance status of 2 or better.
7. Physical exam, CBC and Multiphasic (including electrolytes, BUN, creatinine, total bilirubin, AST, and ALT) must be done within 28 days of PET imaging and demonstrate adequate renal and liver function. Creatinine ≤ 2.5, total bilirubin ≤ 1.5 x upper limit of normal (ULN). AST and ALT ≤ 2.5 ULN.
8. Patient must have a least one lesion greater than 2 cm on standard imaging (CT, MR, octreotide, or dotatate imaging within 8 weeks of the start of the study) that is judged amenable to AMT-PET.
9. Women of child bearing potential must not be pregnant or breastfeeding. A negative urine or blood pregnancy test must be obtained in women with child bearing potential. Men and women with reproductive potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) on study entry and for the duration of study participation.
10. Eligible and consent signed for imaging with AMT PET under protocol 2011-053.

Exclusion:

1. Because of the risk of acute complications from severe diarrhea, patients experiencing more than 12 watery bowel movements per day associated with volume contraction, dehydration, or hypotension, or showing evidence of enteric infection are excluded.
2. Patients are excluded if they had undergone tumor-directed therapy within 3 months.
3. Patients cannot be on a targeted agent (e.g., sunitinib or everolimus) or receiving cytotoxic chemotherapy (e.g., capecitabine or temozolimide). They can't be on telotristat ethyl. Previous use is acceptable if the patient has been off for over one month.

IV. REGISTRATION PROCEDURES

General Guidelines

Eligible patients will be entered on the study centrally at the clinical trials office of the Karmanos Cancer Center/Wayne State University by the study coordinator.

At the time of registration:

- Patients must have signed an informed consent form.
- Confirm that all required prestudy history and physical examination, and laboratory tests have been collected.
- Document demographic information including smoking history. Also document medications.
- Patients should be scheduled for pre-treatment AMT-PET scans if patients have provided appropriate consent.
- Inform patients about all necessary follow-up including laboratory tests and further PET imaging.

Following registration, patients should begin protocol treatment within 7 days of baseline AMT PET imaging. Issues that would cause treatment delays should be discussed with the Principal Investigator, Dr. Anthony Shields at 313-576-8735; shieldsa@karmanos.org, or contact the study coordinators. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The study coordinator should be notified of cancellations as soon as possible.

Registration Process

To register a patient, the following documents should be completed by the research nurse or data manager and faxed or emailed to the study coordinator:

- Copies of required laboratory tests, scans.
- Signed patient consent form.
- HIPAA authorization form.
- Eligibility checklist.
- Completed registration form.

To complete the registration process, the study coordinator will:

- Register the patient on the study

Off-Study Criteria

- Patients will be considered to have gone off of study following the completion of the second AMT-PET scan. They may elect to continue telotristat ethyl therapy under the supervision of their physician as part of standard treatment. Cost of continued standard treatment will be charged to the patient's insurance and patient.

V. TREATMENT PLAN

AMT-PET Imaging

- Scan 1: Baseline within 7 days prior to the start of telotristat ethyl treatment.
- Scan 2: On day 9-14 of telotristat ethyl administration.
- Patients cannot eat protein containing foods for 6 hours prior to the AMT-PET studies, to ensure stable plasma tryptophan and large neutral amino acid levels during the duration of the study. They can have water and soft drinks.
- The final dose of telotristat ethyl on day 9-14 should be taken within 6 hours of the scan and should be taken along with high fat foods, but no protein. This may include oils, olives, low protein breads with margarine. The choice of such foods will be discussed with the patient at the time of enrollment. Note that this dietary restriction only applies for scan 2 since patients need to take telotristat ethyl with fat.
- Blood (approximately 3 tsp) will be drawn to measure drug levels and tumor hormone levels (including serotonin) in the blood prior to each scan. These will be done by the hospital and company laboratories.

Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for telotristat ethyl are described in Section VI. No investigational or commercial agents or therapies other than telotristat ethyl may be administered with the intent to treat the patient's malignancy other than somatostatin analog (long-acting release [LAR], depot.

Agent	Dose	Route	Schedule
Telotristat ethyl	250 mg	Oral	Three times daily for 9-14 days prior to the second scan, with one dose or two doses depending on the time of Scan 2.*

*Patients may elect to stay on telotristat ethyl (250 mg tid) indefinitely following the completion Scan 2 if it is considered to provide benefit by their treating physician as part of the standard of care. As part of the study the patient will received 28 days of drug and may continue to use it and then obtain standard treatment on the agent if desired by the patient and their physician.

Benefits:

Telotristat ethyl (250 mg tid) daily compared to placebo has been shown to improve cancer related diarrhea (Kulke et al., 2017) and may slow tumor growth (Morse et al., 2020).

VI. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE can be

downloaded from the CTEP web site
(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

Reporting Adverse Events

In the unlikely event that any immediate toxicity is found during the course of treatment, it will be recorded and reported as described below. Given the dose of drug, no measurable delayed toxicity is expected.

Reaction	Reporting Obligation for A, B, and C
A. All life-threatening events (Grade 4), which may be due to drug	Within 24 hours (note 1)
B. All fatal events (Grade 5) while on study (or within 24 hour of treatment).	Written report to follow within 10 working days (note 1).
C. First occurrence of any **previously unknown** clinical event (regardless of grade).	(Note 2 and 3)

- Note 1: Telephone number available 24 hours daily: A. Shields page 313-745-5111 beeper 1049, (313)-576-8770 (Recorder after hours). Also may report to SAE@Karmanos.org and ShieldsA@karmanos.org
- Note 2: A list of all known toxicities can be found in the protocol document or consent form.
- Note 3: **Reactions judged *definitely* not treatment-related should not be reported.**
- Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting even if the event is not considered to be related.
- Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol).
- Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the second scan of must be reported.
- Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form.
- Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

Adverse Event (AE) Characteristics

Serious adverse events

A serious adverse event is an undesirable sign, symptom or medical condition which:

1. Is fatal or life-threatening.
2. Required or prolonged hospitalization
3. Results in persistent or significant disability/incapacity
4. Constitutes a congenital anomaly or a birth defect
5. Are medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

Not considered to be serious adverse events are hospitalizations for the:

1. Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
2. Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
3. treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission

Commonly Reported Side Effects of **telotristat ethyl**

From the package insert.

- nausea 13%,
- headache 11%
- increased liver function test (GGT) 9%, possibly indicating liver damage
- depression 9%
- peripheral edema (leg swelling) 7%
- flatulence 7%
- decreased appetite 7%
- fever 7%

In another placebo-controlled clinical trial of patients with carcinoid syndrome diarrhea and less than 4 bowel movements per day, the following additional adverse reactions, not listed above, of abdominal pain (including upper and lower abdominal pain, abdominal distention and gastrointestinal pain) and constipation were reported in at least 5% of patients in the telotristat ethyl treated group and at an incidence greater than placebo. Discontinue telotristat ethyl if severe constipation or severe persistent or worsening abdominal pain develops

Less Common Adverse Reactions:
The following is a list of adverse reactions occurring in less than 5% of patients receiving telotristat ethyl during the 12-week placebo-controlled period of the clinical trial:

Investigations: increased alkaline phosphatase, increased alanine aminotransferase, and increased aspartate aminotransferase.

Fecaloma was reported in one patient treated with telotristat ethyl during the 36-week open-label extension period following the 12-week double-blind period of the trial.

'Attribution' of the AE will be defined by the investigative team

- Definite – The AE *is clearly related* to the study treatment
- Probable – The AE *is likely related* to the study treatment
- Possible – The AE *may be related* to the study treatment
- Unlikely – The AE *is doubtfully related* to the study treatment
- Unrelated – The AE *is clearly NOT related* to the study treatment

VII. MEASUREMENT OF EFFECT: AMT PET SCAN ACQUISTION AND ANALYSIS

Baseline AMT-PET scan will be obtained within 7 days of the start of telotristat ethyl 250 mg po tid and then again 9-14 days after the start of treatment under protocol 2011-053 as described below.

PET imaging will be performed using a GE Discovery STE PET/CT system (GE Medical Systems, Milwaukee, WI), located at the PET Center, Children's Hospital of Michigan. Patients will be imaged in a supine (on their back) position on a PET/CT scanner in a high-sensitivity mode.

Patients cannot eat protein containing foods for 6 hours prior to the AMT-PET studies, to ensure stable plasma tryptophan and large neutral amino acid levels during the duration of the study. The final dose of telotristat ethyl should be taken within 6 hours of the scan and should be taken along with high fat foods, but no protein (as described in the Treatment Plan).

A venous line will be established for injection of AMT tracer (0.1 mci/kg). All PET images will be corrected for attenuation using the CT scan. After injection a CT scan is performed, immediately followed by a 60-minute dynamic PET scan of the area of interest that includes the tumor. The total dose for the PET/CT scan will be in compliance with guidelines for research studies prescribed by the Code of Federal Regulation.

Quantitative assessment of AMT tumor uptake. The AMT uptake in ROIs representing tumor and non-tumor tissue will be characterized in the following two ways:

1. Standardized uptake values (SUVs): The SUV calculation relates tracer concentration in tissue to the dose injected and the subject's mass (SUV = tissue concentration in ROI /injected dose per weight). First, decay-corrected time-activity curves will be generated to evaluate the tumoral accumulation and wash-out of the tracer during the scanning period. Since all subjects receive the same injected dose based upon weight (0.1 mCi/kg), the SUV images will be directly obtained by averaging values from frames of the dynamic image sequence during which time there is the most metabolic product. The timing of these frames will be determined after examination of the time-activity curves to identify the optimal time frame when tracer uptake reaches a plateau. The Standard Uptake Value maximum (SUVmax) will measure the most active pixel in the tumor and the two adjacent planes. Change in SUVmax will serve as the primary aim. Regions of Interest (ROIs) for the SUVmean will be drawn using isocontours set at 50% of the SUVmax. Results will be indicated as percent change in the uptake between the two scans.

2. Compartmental modeling (in tumors with the left ventricle of the heart in the field-of-view)**.** In addition to the semi-quantitative SUV analysis, in tumors where the left ventricle of the heart is in the field-of-view, we will also assess the data with tracer kinetic analysis using a 3-compartment model, as described in our previous studies in lung and breast tumors (Juhasz et al., 2009; 2012). This analysis will allow a more detailed analysis of tumoral tracer transport and trapping parameters at baseline and their changes after TPH inhibitor treatment.

3. Primary endpoint and secondary endpoints:

The proportion of patients who achieved SUVmax reduction of 20% or more between baseline and follow-up will be the primary measurement. We will also assess if the NET is visible above background at baseline and will also quantify the percent difference in AMT uptake between the tumor mass and background. In addition, using time-activity curves, we will also identify the optimal time frame where tumoral AMT uptake peaks. The change in SUVmean will also be measured.

VIII. STATISTICAL PLAN

Design This is a single arm single institution prospective proof-of-concept study. **Primary endpoint** is the proportion of patients who achieved SUVs reduction of 20% or more. The primary endpoint will be reported with a one-sided, 90% confidence limit. The other categorical endpoints will be reported as proportions with two-sided exact 95% confidence intervals. All continuous endpoints will be reported with mean and standard deviation. Paired t test will be used for pre- and post- treatment SUVs if normality assumption holds. The relationship of one PET parameter to another will be visualized with scatter plot and measured using linear regression models. Statistical analysis will be performed using R version 3.3.2. **Power calculation:** This is a Proof-of-Concept trial where the goal is to demonstrate the feasibility and to show the proportion of patients who achieved SUVs reduction is at least 0.2 or higher. Hence, we will calculate the minimum sample size to achieve a confidence lower limit no less than 0.2. A sample size of 6 produces a one-sided 90% lower-limit confidence interval at (0.201, 1) using Clopper-Pearson formula when the expected proportion is 0.5. **Study Duration**: The accrual rate is 6/year and minimum follow -up for each patient will be 3 months. The study will require 15-18 months to complete.

IX. DATA AND SAFETY MONITORING/STUDY AUDITS/STUDY ETHICS

Data and Safety Monitoring

1. Scheduled meetings will be held monthly or more frequently depending on the activity of the protocol. These meetings will include the protocol investigators and research staff involved with the conduct of the protocol.
2. During these meetings the investigators will discuss:
    - Safety of protocol participants (adverse events and reporting)
    - Validity and integrity of the data (data completeness on case report forms and complete source documentation)

- Enrollment rate relative to expectation of target accrual, (eligible and ineligible participants)
- Retention of participants, adherence to the protocol and protocol deviations
- Protocol amendments

3. Data and Safety Monitoring Reports (DSMR) of the research meetings will be completed by the Study Coordinator and submitted to the Data and Safety Monitoring Committee quarterly for review.
4. The Barbara Ann Karmanos Cancer Institute, Data and Safety Monitoring Committee (DSMC) provide the primary oversight of data and safety monitoring for KCI Investigator-initiated trials.

Data Management

Study data including patient images and blood sample results will be maintained by the Shields' laboratory. In addition, a KCI CTO monitor specialist will remotely review the clinical trial data. Frequency of monitoring will be based on accrual but will occur at least once every 2 months if a patient has been enrolled. Monthly screening and enrollment logs will be sent to the KCI lead Study Coordinator.

Study Audits

Authorized representatives of FDA, a regulatory authority or Wayne State University Institutional Review Board (IRB) may visit the center to perform audits or inspections, including source data verification. The investigator should contact Clinical Trials Office immediately if contacted by a regulatory agency about an inspection at his center regarding this study.

Ethics

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

The final study protocol, including the final version of the Written Informed Consent Form, must be approved in writing by Wayne State University IRB.

The principal investigator is responsible for informing the Wayne State University IRB of any amendments to the protocol. The protocol must be re-approved by the IRB annually. Progress reports and notifications of serious, unexpected adverse drug reactions will be provided to the IRB. The Principal Investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product.

The principal investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. In accordance with

the Health Information Portability and Accountability Act (HIPAA), the Written Informed Consent Form must include a subject authorization to release medical information to Karmanos Cancer Institute, Wayne State University, the Detroit Medical Center, University Physician Group, or McLaren Health Care or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

The principal investigator must store the original, signed written informed consent form. A copy of the signed written informed consent form must be given to the subject.

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