AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6687

A Phase 2, Multicenter Evaluation of ^{18}F-Fluoride PET as a Pharmacodynamic Biomarker for Dasatinib, a Src Kinase Inhibitor, in Men With Castration-Resistant Prostate Cancer and Bone Metastases (BMS #180-279)

Agent Name: ^{18}F-fluoride NSC number: REMOVED IND number: REMOVED

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Participating Institutions
All participating sites are members of the Department of Defense-sponsored Prostate Cancer Clinical Trials Consortium and are ACRIN-approved institutions.

PARTIAL PROTOCOL—CONTACT ACRIN PROTOCOL DEVELOPMENT AND REGULATORY COMPLIANCE FOR A COMPLETE PROTOCOL

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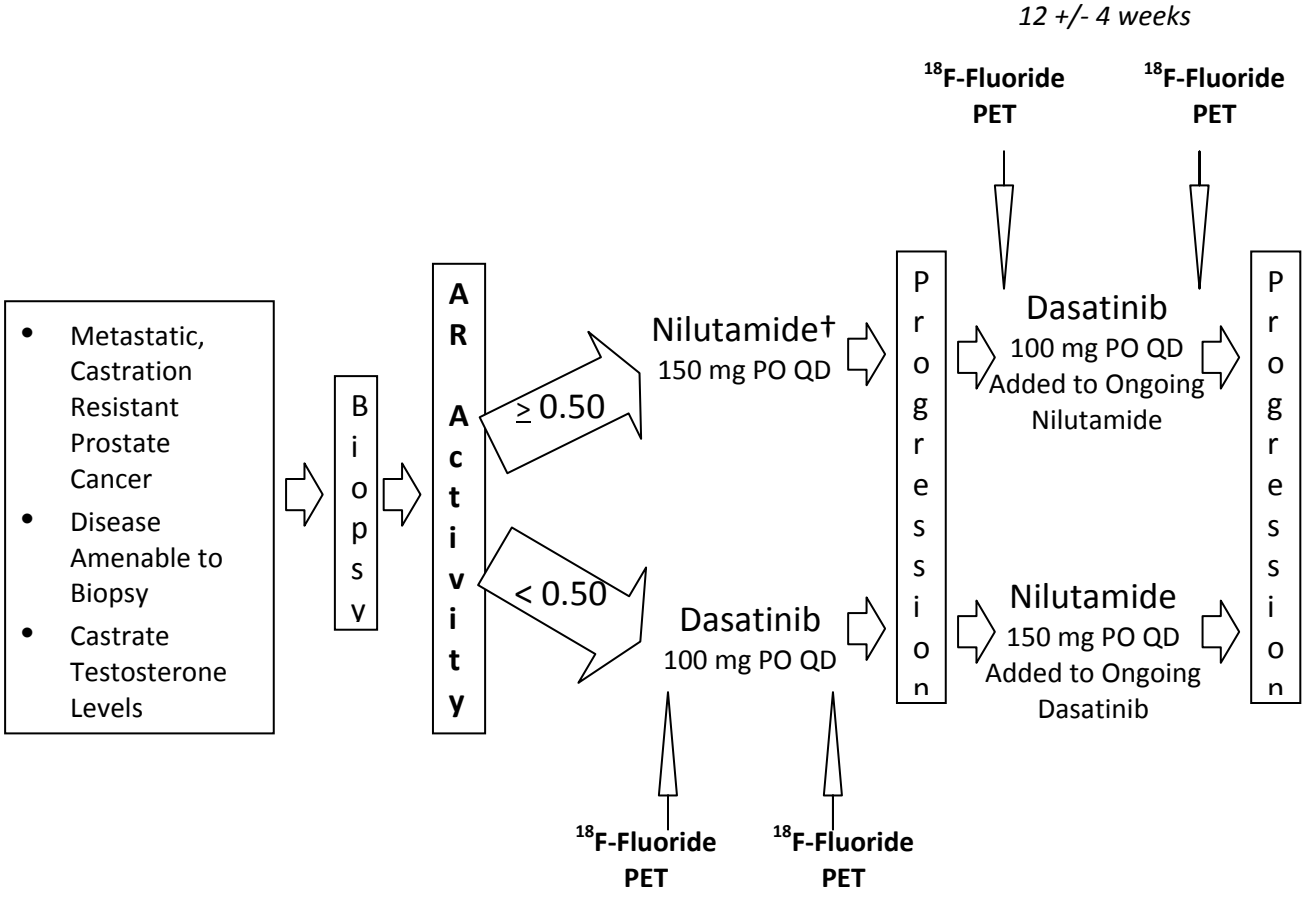
SCHEMA*



***** This Schema reflects the procedures scheduled for the Febbo study—"Genomic Guided Therapy with Dasatinib or Nilutamide in Metastatic Castration-Resistant Prostate Cancer"—and also includes the imaging scan time points of this ACRIN 6687 study (see ^{18}F-fluoride PET-related arrows related to patients undergoing the administration of dasatinib only).

† Patients on the nilutamide-only arm of the therapeutic trial are not eligible for this companion imaging protocol, as the patient must be receiving dasatinib to be eligible. However, if a patient crosses-over from nilutamide at the time of progression to add dasatinib therapy, he may be eligible for this ^{18}F-fluoride PET imaging protocol if the patient meets the eligibility criteria.

THERAPEUTIC STUDY (FEBBO PROTOCOL) OVERVIEW

The following protocol is a companion imaging protocol to accompany the therapeutic protocol designed by Dr. Phillip G. Febbo of the University of California, San Francisco. His study is entitled "Genomic Guided Therapy with Dasatinib or Nilutamide in Metastatic Castration-Resistant Prostate Cancer" (BMS Study #CA 180-263). Dr. Febbo's therapeutic protocol, supported through the Department of Defense and Bristol-Meyers Squibb, will require biopsy of an easily-accessible metastatic prostate cancer lesion for laboratory testing with cDNA microarrays. His laboratory has developed a reproducible and portable signature for androgen receptor (AR) activity, which can be used to identify individual AR activity within prostate cancer specimens providing a means to individualize therapy. His work thus far suggests that patients with low AR activity may have high levels of Src activity, and these patients will be targeted with dasatinib, a known Src kinase inhibitor. Patients with persistently high AR activity will be treated with nilutamide. As there is compelling pre-clinical evidence of interactions between the Src pathway and AR signaling, patients failing either single agent treatment will be treated with the combination of nilutamide with dasatinib and followed again for progression.

Our companion imaging protocol, entitled "A Phase 2, Multicenter, Evaluation of ^{18}F-Fluoride PET as a Pharmacodynamic Biomarker for Dasatinib, a Src Kinase Inhibitor, in Men With Castration-Resistant Prostate Cancer and Bone Metastases," will allow eligible patients currently enrolled in Dr. Febbo's therapeutic trial and receiving dasatinib to undergo ^{18}F-fluoride PET imaging. This includes patients genetically indicated to initial dasatinib-alone treatment, as well as those patients who may crossover at the time of progression to have dasatinib added to nilutamide. Patients receiving nilutamide alone will not be eligible for our companion imaging protocol.

IMAGING COMPANION STUDY (ACRIN 6687) OBJECTIVE/SPECIFIC AIM

To determine whether changes in regional fluoride incorporation, measured by ^{18}F-fluoride PET (SUV and K_i), will occur in both castration-resistant prostate cancer bone metastases and normal bone as a response to treatment with dasatinib.

ELIGIBILITY *(see Section 6.0 for details)*

Men with bone-metastatic castration-resistant prostate cancer (serum testosterone < 50 ng/dl) who are participating on a separate therapeutic clinical trial (Febbo study – "Genomic Guided Therapy with Dasatinib or Nilutamide in Metastatic Castration-Resistant Prostate Cancer") and receiving dasatinib as therapy are eligible for this companion ^{18}F-fluoride PET imaging protocol. Participants from the Febbo trial receiving nilutamide only will not undergo ^{18}F-fluoride PET imaging.

SAMPLE SIZE

Total of twenty-four (24) patients with castration-resistant prostate cancer bone metastases will be enrolled in this companion imaging biomarker study. It is anticipated that accrual will be completed in 1.5 years with minimum of sixteen (16) patients enrolled in a year. A maximum of six (6) institutions will be participating in this trial.

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1.0 ABSTRACT

This protocol for human research study is conducted according to United States and international standards of Good Clinical Practice (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (e.g. Title 45, Part 46 Code of Federal Regulations) and the American College of Radiology Imaging Network (ACRIN) research policies and procedures.

Prostate cancer is the most commonly diagnosed malignancy for men in the United States of America and is second in cancer-related mortality only to lung cancer. Although earlier diagnosis, attributable to increased screening, has led to the discovery of many potentially "curable" lesions, approximately 30-40% of patients will ultimately relapse after definitive local surgery or radiation. Eventually these patients will develop metastatic prostate cancer that most commonly manifests in bone as osteoblastic lesions. Primary treatment of these metastases includes androgen deprivation therapy for hormone-sensitive disease and chemotherapy for more advanced castration-resistant metastatic disease. However, treatment of patients with castration-resistant bone metastases with zoledronate, an intravenous bisphosphonate, has also been shown to decrease time to and proportion of patients with skeletal-related events.

Although most prostate cancer bone metastases are osteoblastic in nature, there is still a very strong osteolytic component that is ongoing. This is evident as approximately 60-70% of patients with bone metastases will have an elevation in the N-telopeptide (uNTx) of type I collagen excreted into the urine. This biomarker for bone turnover has had prognostic ability for both SREs and death[1–4] and defines a subset of patients that will benefit from treatment with bisphosphonates.[5] Normalization of uNTx in response to treatment improves these outcomes,[6] suggesting that inhibition of this uncoupled lytic process may also have effects against prostate cancer growth, progression, and may also decrease skeletal morbidity. Thus, novel agents that target osteoclast activity in addition to having direct antitumor effect may improve overall outcomes for patients with bone metastatic prostate cancer.

Dasatinib [SPRYCEL®] is an orally available, potent, broad spectrum ATP-competitive inhibitor of multiple tyrosine kinase/kinase ffamilies; BCR-ABL, c-KIT, PDGF receptor β (PDFGRβ) and EPH receptor kinases, each of which has been linked to multiple forms of human malignancies. Due to its ability to inhibit BCR-ABL, it is currently FDA approved for patients with imatinib-refractory chronic myelogenous leukemia or with Philadelphia chromosome-positive acute lymphoblastic leukemia. Inhibition of Src and the Src Family Kinases (SFKs) has potential to offer both antitumor and anti-osteolytic effects for a patient. Our phase II study in patients with castration-resistant metastatic prostate cancer confirmed that dasatinib may have some cytostatic effect directly against the tumor. However, even more convincing was the effect on bone turnover markers, i.e. alkaline phosphatase and uNTx. A dramatic inhibition of osteolysis was seen with dasatinib as measured by significant decreases in uNTx levels in the vast majority of patients, regardless of whether the patient was on a bisphosphonate or not. Most interesting, however, is the fact that patients with persistantly elevated uNTx levels while on a bisphosphonate, normalized their levels in response to treatment with dasatinib.[7]

We assume that this notable decrease in uNTx is directly related to inhibition and perhaps even apoptosis of osteoclasts from Src kinase inhibition. However, we do not know whether this process affects both normal bone and bone metastases equally or whether there is preferential activity at sites of tumor; the question remains as to whether inhibition of Src has more generalized effects on the bone or whether there is significant directed antitumor activity in combination with systemic bone effects. It is important to learn more about this process to improve our understanding of Src biology in prostate

cancer, better understand the pharmacodynamics of dasatinib, and direct future study of dasatinib as an antitumor agent, anti-osteolytic agent, or both.

Current methods of imaging bone do not provide adequate information to discern the activity of an agent on either normal bone or bone metastases, much less discern therapeutic effect between the two. They also lack in prognostic capability. CT/MRI scans only provide anatomic information and since patients with prostate cancer often lack measurable disease, the commonly used RECIST criteria are usually not applicable. Bone scintigraphy can identify changes in the bone stroma through local bone turnover, but they do not offer information on tumor activity. Specifically, bone scintigraphy images the osteoblastic reaction to bone metastases, however, the lack of quantification and spatial detail limit the utility of bone scintigraphy as a biomarker. It is clear that we require better imaging modalities to determine tumor activity and treatment response to prognosticate and select therapy for patients with bone metastatic prostate cancer.

^{18}F-fluoride is an alternative agent for imaging new bone formation with PET and can assess changes both in bone metastases as well as normal bone.[8–10] In serial scans with dynamic analysis, the University of Washington cancer imaging group has found K_i (net plasma clearance of tracer to bone mineral) as well as K_1 (fluoride delivery) to be significantly higher in breast cancer bone metastases when compared to normal bone.[11] This imaging modality may be superior to ^{18}F-FDG PET for prostate cancer, since the bone metastases are primary osteoblastic. Osteoblastic metastases tend to exhibit a high rate of fluoride incorporation[12] and may have low FDG uptake.[13] Additionally, ^{18}F-fluoride PET has improved sensitivity and specificity when compared to standard ^{99m}Technetium-MDP bone scintigraphy, and importantly, PET offers the ability for rigorous quantification.[12–14]

^{18}F-fluoride PET is also capable of capturing the effect of bisphosphonate therapy on regional bone metabolism (K_i) and by measuring fluoride delivery (K_1), infer blood flow in normal bone[15,16] and bone metastases.[11] Thus, a response to therapy can be quantifiably described in these patients. Although the relative ratio of bone formation to bone destruction is increased in these patients, there is still a significant decrease in K_i since osteoblastic activity is decreased due to its tight coupling to the decrease in osteoclastic activity from bisphosphonate treatment. Since fluoride is a small molecule, it is readily permeable across capillaries and cell membranes; therefore its delivery is limited largely by blood flow, thus K_1 can serve as an indirect measure of angiogenesis. K_1, however, is not significantly altered in patients receiving bisphosphonate therapy, but could be with other agents that affect angiogenesis and blood flow. Preliminary data in breast cancer suggest that fluoride K_1 and K_i can be independently and accurately measured for both normal bone and bone metastases.[11]

In this study, we propose to use ^{18}F-fluoride PET in patients undergoing treatment with dasatinib to better understand the affect of the drug on both bone metabolism as well as blood flow, an indirect measure of angiogenesis. Since dasatinib inhibits Src, we anticipate there will be a decrease in osteolysis, resulting in decrease in osteoblastic activity and resultant decrease in K_i. Since Src inhibition may have antiangiogenic effects, we anticipate a decrease in K_1 as well. These changes are apt to happen systemically in the non-affected bone; however, it will be important to note whether there is a dramatic effect preferentially at sites of bone metastases as a result of direct antitumor effect and extensive bone remodelling.

The ability to quantify changes in fluoride kinetics in response to treatment is important for the goal of better response evaluation. Thus, ^{18}F-fluoride PET should capture biologic changes that result directly from inhibition of the Src axis both in normal bone and potentially in bone metastases in a quantitative fashion. As an exploratory hypothesis, we believe that patients that have dramatic changes measured by

^{18}F-fluoride PET in bone metastases, as a result of dasatinib treatment, may respond better to therapy with dasatinib and have longer progression-free survival. We will image patients undergoing treatment with dasatinib with ^{18}F-fluoride PET both before and 12 weeks after initiation of therapy to capture the net effect on bone metabolism and blood flow. As a result, we will be able to begin to explore whether ^{18}F-fluoride PET has potential as a prognostic and/or treatment response biomarker.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Men With Prostate Cancer Bone Metastases Require Treatment

Approximately 65% to 75% of patients with advanced prostate cancer will harbor osteoblastic bone metastases.[18] Although standard treatments including androgen deprivation and docetaxel chemotherapy both have efficacy against the tumor, skeletal morbidity remains a major problem for these patients. This morbidity is commonly manifest as skeletal-related events (SREs), which included pathologic fracture, need for surgery to bone, need for radiation to bone, and spinal cord compression. However, bone pain, need for analgesic usage, hypercalcemia, decreased quality of life, and overall shortened survival are other common findings in these patients with bone metastases. Zoledronate, an intravenous bisphosphonate, induces apoptosis in osteoblasts, therefore, decreasing osteolysis, and decreasing the risk of SREs and also extends the time to the first SRE.[19]

2.2 Bone Turnover Markers Have Prognostic Significance for Men With Bone Metastases

Although men with prostate cancer harbor mostly osteoblastic metastases, there is still a very large lytic component that leaves men at risk for significant skeletal morbidity. This bone turnover can be measured by urinary excretion of N-telopeptide, the terminal end of type I collagen, a substance that offers tensile strength for bone. For men with bone metastases, elevation in uNTx, is a measure of the uncoupling of break-down of bone with build-up of bone. This uncoupling, leads to preferential break-down of bone and accelerated bone turnover. This elevation of uNTx is seen in approximately 60% to 70% of men with bone metastases. Previous studies have shown an elevation in uNTx to confer a poor prognosis, as measured by skeletal complications, disease progression, and overall survival.[1-4] However, patients with high uNTx levels may have improved survival when interventions are made with bisphosphonates, such as zoledronate.[5] Additionally, patients with elevated uNTx who normalize levels within 3 months after treatment with zoledronate have improved survival and decreased risk of SREs when compared to patients with persistently elevated uNTx.[6]

2.3 Inhibition of Src With Dasatinib Has Efficacy Against Prostate Cancer

Src kinase is highly expressed both on castration-resistant prostate cancer cells and osteoclasts. Thus, we performed a phase 2 study with the hope of dual antitumor and anti-osteolytic effects. Men with rising PSAs and castration-resistant metastatic prostate cancer were treated with dasatinib dosed at 100 mg po bid, 70 mg po bid, and 100 mg po qd. Our study chair, Yu EY et al. reported the results of the bid-dosed patients.[7]

Antitumor efficacy was demonstrated as 20 of 47 patients (43%) and 9 of 47 (19%) had lack of disease progression demonstrated by bone/CT scans at 12 and 24 weeks, respectively. Dasatinib modified PSA kinetics and 1 out of 43 evaluable patients had a confirmed $\geq$ 50% PSA decline. That patient has now been on continuous dasatinib for more than 2 years with stable disease on scans and a sustained PSA response. PSA doubling time was prolonged in 34 of 43 patients (79%). Among treated patients, 41 had bone metastases and 39 underwent week 12 bone scan reassessments. One of 41 showed improvement. Stable disease was identified in 23 of 41 (49%). Of the subgroup of patients who reached the 24-week

assessment, 9 of 14 had stable disease. Twenty-three (23) patients had at least one RECIST-evaluable lesion at baseline, and 20 of these patients had at least one on-study tumor assessment. One patient had an unconfirmed PR in his metastatic liver lesions. Twelve (12) of 23 patients had stable disease. In summary, dasatinib has direct antitumor effect, although it appears that for most patients, it may be more cytostatic, rather than directly cytotoxic.

Perhaps most remarkable in this study was the significant effect dasatinib had on markers of bone turnover. Alkaline phosphatase was measured in 40 patients and 24 (60%) experienced a decrease in levels: 11 of 21 (52%) who were on a bisphosphonate and 13 of 19 (68%) who were not on a bisphosphonate. Inhibition of osteolysis as measured by a decrease in uNTx levels occurred in 33/41 (80%) patients treated and evaluated. The propotion of patients achieving a ≥40% decline in uNTx by week 12 was 21 of 41 (51%); including those receiving bisphosphonates (52%; 11/21 patients) and not receiving bisphosphonates (50%; 10/20 patients).[7] At baseline 15 patients had above normal levels of uNTx. Of these patients, 75% of those who were receiving a bisphosphonate achieved a reduction in uNTx levels to within normal range. Of these patients who were not receiving bisphosphonates, 45% achieved a reduction in uNTx levels to within normal range.

Given the dramatic effects of dasatinib on markers of bone turnover and its potential cytostatic antitumor effect, it is worth studying the pharmacodynamics of the drug in greater detail. Understanding whether the mechanism of the drug is systemic throughout normal bone or whether the drug truly has preferential activity at the sites of bone metastases will be important. Using appropriate biomarkers to determine this will help direct future study of the drug as a primary antineoplastic, bone remodeling and stabilization agent, or both.

2.4 Determining Response to Treatment for Patients With Prostate Cancer Is Challenging and Fraught With Problems

A clinically meaningful prostate cancer treatment response has been notoriously difficult to define, and there is no uniformly accepted modality. This is partially due to the fact that 60% to 70% of prostate cancer patients lack measurable soft tissue disease, and the disease tends to be bone-dominant. Bone scintigraphy measures changes in the stroma, not decreased activity of metastatic tumor cells. Thus, bone scintigraphy can be confounded by multiple factors, i.e. initial treatment flare, healing bone, and long-term remodeling of bone.[20] Additionally, bone scintigraphy is limited by a lack of quantitative ability. Although a metastatic lesion may be improving as a response to therapy, bone scintigraphy may not accurately reflect that, and can sometimes even look worse as a result of healing bone.

Since our current standard imaging methods are suboptimal for accurately defining treatment effect or assessing biological tumor response, a combination of laboratory and clinical parameters are often used to determine response to therapy. PSA decline of 50% or greater is often utilized as an endpoint in clinical trials,[21] and some have found a correlation with improved survival in retrospective studies.[22,23] However, this marker has not been uniformly accepted, and the FDA does not accept this endpoint as a surrogate for survival. Pain palliation, improvement in quality of life (QOL), and decrease use of analgesic intake are also utilized as endpoints in clinical trials. However, these endpoints are subjective, and they also do not necessarily correlate with hard endpoints, such as survival.

The use of PET as a method of monitoring response to therapy in prostate cancer is appealing. PET imaging relies on differential tumor metabolism of substances such as glucose, acetate, choline, or fluoride. This form of biologic imaging is advantageous as it may immediately reflect the response of tumor to a particular treatment. ^{18}F-FDG is a radioactive tracer commonly utilized in routine PET imaging for malignancies such as lung cancer, but it may lack sensitivity for imaging prostate cancer.[24]

This may be due to a relatively low proliferative rate, and urinary excretion of the radiotracer obscures the prostate and surrounding lymph nodes.[25,26] ^{18}F-FDG also has limited sensitivity for the detection of osseous metastases, as compared to bone scintigraphy, with detection rates ranging from 18% to 65%.[25-27] This may be partially due to the fact that ^{18}F-FDG seems to detect lytic lesions much better than blastic lesions, and prostate cancer bone metastases tend to be osteoblastic in nature.

2.5 Rationale for ^{18}F-fluoride PET Imaging as a Marker of Bone Metabolism and Potential Novel Biomarker for Patients With Bone Metastases

Although ^{18}F-fluoride was the first widely used radiotracer for skeletal scintigraphy, it quickly fell into disuse after the introduction of ^{99m}Technetium-MDP bone scintigraphy. However, ^{18}F-fluoride PET offers many advantages over planar bone scintigraphy. It is quantitative, offering information in regards to local changes in bone biology. It also offers information about normal bone, not just bone metastases. Recent studies with ^{18}F-fluoride PET show improved sensitivity over bone scintigraphy for multiple solid tumors, including prostate cancer; these studies underscore the ability of ^{18}F-fluoride PET to detect osteoblastic lesions, as well as osteolytic lesions and very early small marrow-based metastases, by identifying their accompanying reactive osteoblastic changes, even when minimal.[14,28] Given the fact that prostate cancer tends to harbor osteoblastic metastases, ^{18}F-fluoride PET offers the ability to image the lesions with excellent sensitivity while offering a mechanism of monitoring and quantifying treatment response, especially for novel therapeutics that have bone remodeling effects. With the widespread availability of PET scanners and the improved logistics for the delivery of ^{18}F radiopharmaceuticals, prior limitations to the routine use of ^{18}F-fluoride bone imaging have largely been overcome.

Based upon the kinetic model of Hawkins et al,[16] ^{18}F-fluoride PET is also capable of capturing the treatment effect of bisphosphonate therapy on regional bone metabolism (K_i) and fluoride delivery (K_1), a measure closely related to blood flow, in normal bone.[15] Thus, a response to therapy can actually be quantifiably described in these patients. Although the relative ratio of bone formation to bone destruction is increased in these patients, there is still a significant decrease in K_i since osteoblastic activity is decreased due to its tight coupling to the decrease in osteoclastic activity from bisphosphonate treatment. Since fluoride is a small molecule, it is readily permeable across capillaries and cell membranes; therefore its delivery is limited largely by blood flow, thus delivery (K_1) can serve as an indirect measure of angiogenesis.[11,16] K_1, is not significantly altered in patients receiving bisphosphonate therapy, but might be with other agents that affect angiogenesis and blood flow. Src kinase inhibition with dasatinib has this potential, thus, K_1 may prove to be an interesting measure in our planned study.

2.6 Preliminary Data

In conjunction with the breast cancer research group at the University of Washington, our imaging group has recently shown that quantitative imaging with ^{18}F-fluoride PET is feasible for cancer imaging of bone metastases. With dynamic analysis, the University of Washington cancer imaging group has found K_i (net plasma clearance of tracer to bone mineral) as well as K_1 (fluoride delivery and an indicator bone blood flow) to be significantly higher in breast cancer bone metastases when compared to normal bone.[11] This imaging modality may be superior to ^{18}F-FDG PET for prostate cancer, since the bone metastases are primarily osteoblastic. Osteoblastic metastases tend to exhibit a high rate of fluoride incorporation[12] and may have low FDG uptake.[13] Additionally, ^{18}F-fluoride PET has improved sensitivity and specificity when compared to standard ^{99}mTechnetium-MDP bone scintigraphy.[12,14] Preliminary data in breast cancer suggest that fluoride K_1 and K_i can be independently and accurately measured for both normal bone and bone metastases.[11]

Overall, imaging prostate cancer bone metastases with ^{18}F-fluoride PET provides an ideal method for evaluating an agent, such as dasatinib, expected to affect both normal bone and bone metastases. In particular, we hope to gain pharmacodynamic information with ^{18}F-fluoride PET to gain more insight on the effects of dasatinib both on normal bone and bone metastases. This also offers an opportunity to determine whether ^{18}F-fluoride PET has prognostic and response biomarker potential for patients with bone metastatic prostate cancer.

3.0 STUDY OBJECTIVES/SPECIFIC AIMS

3.1 Primary Endpoint

Determine if changes in regional fluoride incorporation, measured by ^{18}F-fluoride PET (SUV and K_i), occur in both castration-resistant prostate cancer bone metastases and normal bone as a response to treatment with dasatinib.

3.2 Secondary Endpoint

Determine if changes in ^{18}F-fluoride transport (K_1), an indicator of blood flow, and therefore, an indirect marker of angiogenesis, occur in both castration-resistant prostate cancer bone metastases and normal bone as a response to treatment with dasatinib.

3.3 Exploratory Endpoints

3.3.1 Estimate the difference of treatment effects in tumor over normal bone as a response to treatment with dasatinib in terms of changes in regional fluoride incorporation indicators (SUV and K_i) and the blood flow indicator (K_1).

3.3.2 Explore if ^{18}F-fluoride PET parameters (SUV, K_i, and K_1) at baseline and/or change in response to treatment with dasatinib is predictive or prognostic for the likelihood of a skeletal-related event (SRE) and/or duration until a first SRE, bone-metastatic progression-free survival, composite progression-free survival as defined by the Prostate Cancer Working Group 2 (PCWG2)[17] definition, and overall survival.

3.3.2.1 Bone metastasis analysis;

3.3.2.2 Normal bone analysis;

3.3.2.3 Differential analysis.

3.3.3 Compare changes in ^{18}F-fluoride PET (SUV, K_i, and K_1) parameters with changes in urinary N-telopeptide and bone alkaline phosphatase in response to treatment with dasatinib.

3.3.3.1 Bone metastasis analysis;

3.3.3.2 Normal bone analysis;

3.3.3.3 Differential analysis.

3.3.4 Compare ^{18}F-fluoride PET with standard bone scintigraphy obtained both pre-treatment and while on treatment with dasatinib.

3.3.4.1 Assess sensitivity for detection of bone metastases.

3.3.4.2 Report newly discovered ^{18}F-fluoride PET sites, suspicious for bone metastases that are not initially detected by standard bone scintigraphy but subsequently appear at a later time point on bone scintigraphy.

3.3.4.3 Compare ability of ^{18}F-fluoride PET and standard bone scintigraphy to quantify bone metastases treatment response with dasatinib.

Note: No treatment decisions will be based on new lesions discovered solely by ^{18}F-fluoride PET.

3.3.5 Compare pre- versus post-treatment changes in bone metastases discovered by ^{18}F-fluoride PET independently with changes in PSA measures.

4.0 STUDY DRUG INFORMATION

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5.0 STUDY OVERVIEW

Twenty-four (24) patients with castrate (serum testosterone < 50 ng/dl) prostate cancer bone metastases enrolled to receive dasatinib on a separate phase II clinical trial (Febbo protocol included for reference only) will be evaluated in this companion imaging biomarker study. Our goal will be to accrue 16 patients a year to the study (1.5 years for accrual) from a maximum of 6 participating sites. Each participant will undergo procedures as per the separate Febbo protocol.

In summary, an image-guided biopsy of a prostate cancer metastasis will determine whether the participant has an "AR high" or an "AR low" (Src signature which is the inverse of AR high) DNA microarray signature. This information assists in understanding the biology of each individual's mechanism of castration-resistance. In the Febbo therapeutic protocol, if the participant's tumor has an "AR high" signature, he will first receive treatment with nilutamide (Arm A). If an "AR low" (Src signature) pattern is identified, the participant will receive treatment with dasatinib (Arm B). At the time of progression, dasatinib will then be added for participants in Arm A and nilutamide for participants in Arm B.

Each participant will undergo an investigational ^{18}F-fluoride PET scanning prior to initiation of dasatinib therapy (baseline), and again 12 weeks after initiation of dasatinib on ACRIN qualified PET scan. Patients on the nilutamide-only arm of the therapeutic trial are not eligible for this companion imaging protocol, as the patient must be receiving dasatinib to be eligible. However, if a patient crosses-over from nilutamide at the time of progression to add dasatinib therapy, he will then be eligible for this ^{18}F-fluoride PET imaging protocol at that time.

We estimate that we will accrue 12 patients who are on Arm A of the therapeutic study, and another 12 patients who are on Arm B of the therapeutic study, but we will not be strict with that goal. SUV and dynamic analysis, which allows us to estimate K_i and K_1, will be performed on the ^{18}F-fluoride PET studies (at sites of bone metastases and adjacent normal bone). These parameters will be compared individually in each participant to determine change in response to treatment from dasatinib.

Additionally, these parameters will be compared to determine whether there are major differences between normal bone and bone metastases and whether treatment-related changes are preferentially occurring in bone metastases over normal bone. All parameters will be compared directly to PSA (monthly), urine N-telopeptide (uNTx, obtained at baseline and 12 weeks), bone alkaline phosphatase (obtained at baseline and 12 weeks), as well as chest/abdomen/pelvis CT scans and bone scans obtained both at baseline and every 12 weeks thereafter while on study.

The participants will be followed prospectively to determine time to bone metastatic disease progression and time to skeletal-related events (SREs) while on the therapeutic study. Coordinator assessments for progression and SRE endpoints will occur once every 3 months. SREs will be defined as a pathologic

bone fracture (confirmed by x-ray, CT, or MRI), surgery to bone, radiation to bone, or a spinal cord compression (confirmed by CT or MRI). After participants come off the therapeutic study, every 2-month assessments of survival will be performed as part of the Febbo therapeutic study. These data will be collected for the ACRIN study for up to 5 years. ACRIN will have access to these data through a data-sharing agreement.

PET image analysis will be performed by the following methods (see Section 10.0 for additional imaging details):

- *SUV quantification* measures the total concentration of the radioactive label at any given time. A full body sweep will be performed.
- *Compartmental or graphical analysis of dynamic scans.* The dynamic imaging field will be selected to include the most prominent site of bony metastasis at the discretion of the local imaging team, with preference to those regions that include the heart or a major blood vessel. A fixed-size region of interest will encompass the area of maximum uptake on the summed dynamic images (30–60 minutes) in the metastasis, preferentially including the great vessels. Specific measures of interest include: $K_{i,}$ as an indicator of net plasma clearance of fluoride to bone mineral, and K_1, as an indicator of bone blood flow and an indirect measure of angiogenesis.

6.0 PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

Men with bone-metastatic castration-resistant prostate cancer who are participating on a separate therapeutic clinical trial - Febbo study - and who will be receiving dasatinib as therapy are eligible for this companion ^{18}F-fluoride PET imaging protocol. Patients on the nilutamide-only arm (Arm A of the therapeutic trial) are not eligible for this companion imaging protocol initially. However, if a patient crosses-over from nilutamide at the time of progression to add dasatinib therapy, he may be eligible for this ^{18}F-fluoride PET imaging protocol if the patient meets the eligibility criteria.

6.1 Inclusion Criteria

6.1.1 Must be able to provide a written informed consent.

6.1.2 Men 18 years or older with metastatic castration-resistant prostate cancer enrolling onto the Febbo clinical trial with dasatinib therapy (must meet all inclusion criteria for dasatinib treatment study and comply with requirements of that specific clinical trial).

6.1.3 Histologic confirmation of original prostate cancer diagnosis.

6.1.4 Presence of at least one convincing bone metastasis as defined by bone scintigraphy, CT scan (MRI if indicated), or plain X-ray.

6.1.5 Must currently have castrate testosterone levels (< 50 ng/dL) from orchiectomy or maintenance on a LHRH agonist or LHRH antagonist.

6.2 Exclusion Criteria

6.2.1 On the nilutamide-only arm (Arm A of the clinical therapeutic trial);

Note: However, if a patient crosses-over from nilutamide at the time of progression to add dasatinib therapy, he may be eligible for ^{18}F-fluoride PET imaging protocol if he meets all inclusion criteria for this trial.

6.2.2 Any condition that would alter the patient's mental status, prohibiting the basic understanding and/or authorization of informed consent.

6.2.3 A serious underlying medical condition that would otherwise impair the patient's ability to receive treatment and imaging studies.

6.2.4 Expected lifespan of 12 weeks or less.

6.2.5 Extremely poor intravenous access, prohibiting the placement of a peripheral IV line for injection of radiotracer.

6.2.6 Initiation of bisphosphonate therapy less than 4 weeks from the first PET scan.

6.2.7 Radiation treatment to bone less than 4 weeks from first PET scan.

6.2.8 Radiopharmaceutical treatment to bone less than 4 weeks from first PET scan.

6.2.9 Treatment with granulocyte-macrophage colony stimulating factor (GM-CSF) or granulocyte CSF (G-CSF) within 4 weeks prior to first PET scan.

6.2.10 Inability to lie still for the imaging.

6.2.11 Weight > 300 lbs. (due to equipment specifications).

6.3 Recruitment and Screening

Participant enrollment in the imaging study will also occur at maximum of 6 ACRIN-approved sites that are participating in the Department of Defense (DOD) Prostate Cancer Clinical Trials Consortium (PCCTC).

Medical oncologists at each site will identify patients who are eligible to receive dasatinib on the Febbo study – the therapeutic clinical trial. As part of the consenting process for the therapeutic trial, the oncologist or clinical research associate will also discuss with the patient the option to participate in the companion imaging study. If patients express a participation interest, the clinician will present the requirements of the imaging component in more detail and informed consent will be obtained. Each patient will receive proper prostate cancer treatment regardless of whether he chooses to participate in the imaging study component.

The accrual goal is to enroll 16 patients per year with a total of 24 patients enrolled in 1.5 years. Interim analysis and presentation of interim data at a national conference such as ASCO is anticipated approximately 2 years after study initiation with a final publication expected the following year.

If determined to be beneficial, ACRIN will develop participant educational materials about the imaging study for distribution by the oncology clinicians. All materials used for participant recruitment will be reviewed and approved by each institution's Institutional Review Board (IRB).

6.4 Inclusion of Women and Minorities

All eligible male patients will be approached at participating sites, regardless of race or ethnicity. Patients will be recruited from the existing patient population at the participating sites. Participating centers will be constrained based on their general population base and ethnic mix.

Men of all ethnic groups are eligible for this trial. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993, with regard to inclusion of minorities in clinical research, the projected minority accruals are shown in Table 2:

Table 2. Gender and Minority Accrual Estimates

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	0	23	0	23
Ethnic Category: Total of all subjects	0	24	0	**24**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	2	0	2
Black or African American	0	2	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	0	20	0	20
Racial Category: Total of all subjects	0	24	0	**24**

7.0 SITE SELECTION

7.1 Institution Requirements

The potential sites for this study are both DOD PCCTC and ACRIN-approved institutions that meet qualifications and that have access to local or commercial supply of the ^{18}F-fluoride agent according to the parameters of the NCI-sponsored IND for participating in this study. This will ensure that the ^{18}F-fluoride tracer arrives successfully to the site and can be handled appropriately. For any sites approved to manufacture their own ^{18}F-fluoride, the site must provide CMC data and Letter of Authorization (LOA), along with Drug Master Files (DMFs) to FDA, NCI/CIP and ACRIN regulatory personnel as part of the site qualification process.

Each institution must complete a Protocol Specific Application (Appendix II; available online at www.acrin.org/6687_protocol.aspx). The Protocol Specific Application is reviewed by the ACRIN Institutional Participants Committee and only sites with an approved Protocol Specific Application can activate the study.

In addition, sites must complete the ACRIN Qualifying Application for PET or PET/CT scanner(s) to be used on the trial. This information, along with other supplemental materials are available on the ACRIN web site, www.acrin.org/6687_protocol.aspx. This process includes submitting test images to ACRIN for review and approval. Centers that have received PET or PET/CT qualification approval for other ACRIN studies may be eligible for expedited qualification. Institution can begin enrolling participants on this study only after they have received notification that all application requirements have been met.

All regulatory documentation required for this study must be submitted to ACRIN headquarters (via fax: 215-717-0936, ATTN: ACRIN Protocol Development and Regulatory Compliance Department)

7.2 IRB Approval and Informed Consent Form

All institutions must have study-specific Institutional Review Board (IRB) approval for the protocol and informed consent form (ICF). (The ICF is included in this protocol as Appendix I.) The investigator and

the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB at the institution. A copy of the IRB approval letter and a copy of the IRB-approved, site-specific ICF must be delivered to the trial monitor to review the approved form and to keep on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: Protocol Development and Regulatory Compliance Department) prior to registering the first participant.

7.3 Accrual Goals and Monitoring

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Total target accrual for this study is 24 participants. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving any recruitment barriers.

The ACRIN Steering Committee regularly reviews the overall trial accrual and may request information about a trial's accrual performance to better understand general accrual barriers or issues. Accrual and safety information will be presented to the ACRIN Data Safety and Monitoring Committee (DSMC) at regularly scheduled meetings thereof; the DSMC may, at its discretion, re-evaluate the study with respect to feasibility or the need for additional participating institutions.

8.0 DATA MANAGEMENT/ONLINE REGISTRATION

8.1 General

8.1.1 The ACRIN web address is www.acrin.org**.**

8.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at ACRIN in Philadelphia, PA.

8.1.3 Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the DMC before attempting a re-registration. A DMC contact list is located on the ACRIN web site for each protocol.

8.2 Clinical Data Submission

8.2.1 Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize participants. Upon successful registration, an ACRIN case-specific calendar will be generated. This calendar lists all forms and designated reports required by protocol along with form due dates at ACRIN's Data Management Center (DMC). If the confirmation e-mail is not received, the enrolling person should contact the DMC before attempting a re-

registration. The calendars are available 24 hours a day on the ACRIN web site and will be updated as the study proceeds to reflect data that have been received, due dates for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling. The investigative site is required to submit data according to protocol as detailed on each participant's ACRIN calendar. A DMC contact list is located on the ACRIN web site for each protocol.

8.2.2 To submit data via the ACRIN web site, the appropriate investigator-designated research staff will log in to the Data Center through the ACRIN web site with pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, data that are out of range, or in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the "Complete Form Submission" button is depressed.

8.2.3 Once data entry of a form is complete, and the summary form is reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form" button on the form summary screen and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data generated and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the DMC for resolution of the submission.

8.2.4 If technical problems prevent access to the Data Center web site, sites will be unable to enter data. The site RA or investigator should notify the DMC if a problem with the Data Center is encountered. All sites will be notified through an ACRIN broadcast message when access to the web data entry is unavailable and the estimated time when access will be restored. The investigative site should wait until access is restored to submit data.

8.3 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

8.4 Electronic Data Management

8.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server; the data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Biostatistics and Data Management Center (BDMC) that are more comprehensive than those built into the web-based data entry screens. The BDMC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. The validation program generates a log of errors which is managed by the DMC Data Manager (DM). The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time DMC spends resolving problems. All communication with the participating sites is handled by the DMC.

8.4.2 If missing or problematic data is detected, the DM sends an Additional Information Request (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DM updates the participant's data submission calendar with the Z1 due date to notify the site RA or investigator of when a response is expected. The calendar will be updated upon receipt of the query response.

8.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. This report lists data items (e.g. forms, reports, and images) that are delinquent. It is distributed at regular intervals via the electronic mail system to both the RA and the investigator at each site. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Forms Due Reports may be sent on an as-needed basis in addition to past due reports. The site investigator or RA may use the Forms Due and Future Due Reports as a case management tool. At any time, sites may run their own Forms Due Reports using the Site Operations Tool on the ACRIN web site.

8.6 Data Quality Assurance

8.6.1 The Biostatistics Center (BC) at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database at the DMC. The transfer of data between the DMC and the BC have been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

8.6.2 Data will be monitored to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the DMC will contact the site to resolve the problem. The ACRIN Protocol Development and Regulatory Compliance (PDRC) Department will be involved in this process as needed. If the BDMC and PDRC cannot reconcile the problem with the site,

it will be brought to the ACRIN Quality Assurance (QA) Committee for further discussion and resolution.

9.0 STUDY PROCEDURES

Participants with castration-resistant bone metastatic prostate cancer planning to receive dasatinib on the DOD-sponsored therapeutic clinical trial will undergo two (2) PET scans, using the investigational ^{18}F-fluoride as a tracer to detect metastatic sites and evaluate normal bone: 1) within 7 days prior to treatment and 2) at 12 weeks (± 4 weeks to accommodate for scheduling in the research PET suite) after initiation of dasatinib therapy. All PET scans must be performed on equipment specifically qualified for this trial using the same image acquisition parameters as described in section 10.0 and on the ACRIN 6687 web site, www.acrin.org/6687_protocol.aspx. Study PET scans will be completed on the same ACRIN-qualified PET scanner at each imaging visit.

9.1 Visit 1: Eligibility and Registration Visit

Participants enrolled into the Febbo study and will receive dasatinib treatment are potential participants for this study. The following procedures must be completed during the visit:

- Obtain a signed informed consent;
- Assess for eligibility as outlined in Section 6.0;
- Review medical history;
- Conduct a physical examination;
- Document concomitant medications;
- Review the standard clinical test results which were completed within 60 days prior to enrollment, which includes:
  - Metastatic biopsy;
  - Bone scan;
  - CT and/or MRI scan(s) of chest, abdomen, and pelvis;
  - Any other scans performed for evaluation, e.g. x-rays, if indicated;
  - Prostate-specific antigen (PSA) measures;
  - Bone alkaline phosphatase;
  - Urine N-telopeptide.

NOTE: Patients on the nilutamide-only arm (Arm A of the therapeutic trial) are not eligible for this companion imaging protocol. However, if a patient crosses-over from nilutamide at the time of progression to add dasatinib therapy, he will then be eligible for this ^{18}F-fluoride PET imaging protocol if all inclusion criteria for this study have been met.

9.2 Visit 2: Pre-Treatment ^{18}F-Fluoride PET Scan - Within 7 Days Prior to Treatment Initiation With Dasatinib

- Place an intravenous catheter (IV), 18 or 20 gauge is preferred, in a vein of the participant's arm;

- Inject ^{18}F-fluoride (0.14 mCi/kg of radiotracer up to a maximum of 10 mCi) into the IV in the participant's arm;
- A saline flush should follow the ^{18}F-fluoride injection;
- Immediately following the ^{18}F-fluoride injection, perform the 60 minute dynamic imaging;
- Perform attenuation scan once participant is comfortably placed in the PET scanner per imaging Section 10.1;
- Perform a static whole body image from mid-thigh to head after the 60 minute dynamic and either CT or external source attenuation correction scan;

  NOTE: Imaging will take approximately 90 to 120 minutes, depending on the device and procedure for attenuation correction; For details for the dynamic imaging protocol and timing, please refer to ACRIN web site, www.acrin.org/6687_protocol.aspx.
- Obtain a torso survey with emission scanning, imaging for 5 minutes per 15 cm axial section covered.
- Obtain vital signs;
- Assess for adverse events (AEs) prior to leaving the PET suite.

9.3 Visit 3: Telephone Contact – After 24-Hour Period from the ^{18}F-Fluoride PET Scan

To be completed after 24-hour period from the ^{18}F-fluoride PET scan for assessment of any adverse events for the investigational ^{18}F radiotracers.

- Contact participant via phone to assess for AE that may have occurred within the 24 hours after the PET scan;
- Assess for any changes to concomitant medications provided at Visit 1.

9.4 Visit 4: Post-Treatment ^{18}F-Fluoride PET Scan - 12 Weeks After Treatment Initiation With Dasatinib (± 4 Weeks To Accommodate Scheduling of the PET Suite)*

- Review the standard clinical test results which includes:
  - Physical examination;
  - Metastatic biopsy, if additional biopsy was ordered;
  - Bone scan;
  - CT and/or MRI scan(s) of chest, abdomen, and pelvis;
  - Any other scans performed for evaluation, e.g. x-rays, if indicated;
  - PSA measures;
  - Bone alkaline phosphatase;
  - Urine N-telopeptide.
- Place an IV, 18 or 20 gauge is preferred, in a vein of the participant's arm;
- Inject ^{18}F-fluoride (0.14 mCi/kg of radiotracer up to a maximum of 10 mCi) into the IV in the participant's arm;
- A saline flush should follow the ^{18}F-fluoride injection;

- Immediately following the ^{18}F-fluoride injection, perform the 60 minute dynamic imaging;
- Perform attenuation scan once participant is comfortably placed in the PET scanner per imaging Section 10.1;
- Perform a static whole body image from mid-thigh to head after the 60 minute dynamic and either CT or external source attenuation correction scan;

  NOTE: Imaging will take approximately 90 to 120 minutes, depending on the device and procedure for attenuation correction; For details for the dynamic imaging protocol and timing, please refer to ACRIN web site, www.acrin.org/6687_protocol.aspx.
- Obtain a torso survey with emission scanning, imaging for 5 minutes per 15 cm axial section covered.
- Obtain vital signs;
- Assess for AEs prior to leaving the PET suite.

* Should clinical progression (including disease progression, pain, etc.) occur prior to the 12-week imaging time point, the study leadership encourages the site PI to recommend completion of the second ^{18}F-fluoride PET scan prior to the participant going off study, if the participant is physically capable of completing the scan. However, this intermittent time point should occur only in those cases of clinical progression.

9.5 Visit 5: Telephone Contact – After 24-Hour Period from the ^{18}F-Fluoride PET Scan

To be completed after 24-hour period from the ^{18}F-fluoride PET scan for assessment of any adverse events for the investigational ^{18}F radiotracers.

- Contact participant via phone to assess for AE that may have occurred within the 24 hours after the PET scanner;
- Assess for any changes to concomitant medications provided at Visit 1 & 3.

9.6 Follow Up: Standard Clinical Follow Up on Febbo Trial, Survivorship Data Collected Up to 5 Years for ACRIN Trial

Participants will be followed by the treating physician per the institution's standard of care. The Febbo therapeutic study will check on survival status of each participant once every 2 months after the participant has come off treatment. These data will be collected for the ACRIN study for up to 5 years. ACRIN will have access to the survival data through a data-sharing agreement between Duke and ACRIN.

9.7 Off-Study Criteria

If a participant is not able to receive both the pre-treatment and the post-treatment ^{18}F-fluoride PET scans, the participant will be replaced on study. If both scans are performed, the primary endpoint will be assessable, and there will be no need to replace the participant should the participant be considered lost to study follow-up later.

In cases of clinical progression (including disease progression, pain, etc.) that occur prior to completion of the 12-week imaging time point and that lead the participant to discontinue treatment, the study leadership encourages the site PI to recommend completion of the second ^{18}F-fluoride PET scan prior to

the participant going off study, if the participant is physically capable of completing the scan. In these cases, the participant will not need to be replaced on the trial.

The following list outlines sample instances when the participant will not be asked to complete the post-treatment ^{18}F-fluoride PET scan and will therefore need to be replaced as study participants (including treatment components that may compromise the ability to assess response to the dasatinib agent):

- Participants may voluntarily withdraw from the study at any time.
- Participant is non-compliant with treatment regimen with dasatinib, imaging protocol, or sample acquisition.
- At the discretion of the investigators, participants may be removed from the study if the physician feels it to be in their best medical interest.
- Participants may be removed because radiation therapy is necessary during the interval between PET scans.
- Participant receives another systemic therapy for prostate cancer before the second PET is obtained.
- Participant misses more than four weeks of dasatinib during the interval between PET scans.
- Participant receives GM-CSF or G-CSF during the interval between the first and second PET imaging studies (see Section 6.2 for exclusion criteria).

9.8 Study Procedures Table

Study Procedures	VISIT 1	VISIT 2 Pre-treatment PET Scan (Within 7 Days Prior to Dasatinib)	VISIT 3 Telephone Contact (24 Hours After PET Scan)	FEBBO TRIAL: DASATINIB TREATMENT[3]	VISIT 4 Post-treatment PET Scan (12 Weeks After Treatment Initiation)	VISIT 5 Telephone Contact (24 Hours After PET Scan)	FOLLOW UP: DATA OBTAINED FROM FEBBO TRIAL
Informed consent	X						
Eligibility assessment / ACRIN web registration	X						
Past & current medical history± and physical exam	X[1]				X[1]		
Bone scan	X[1]				X[1]		
CT scan of chest, abdomen, and pelvis	X[1]				X[1]		
Prostate-specific antigen (PSA)	X[1]				X[1]		
Bone turnover markers (urine N-telopeptide and bone alkaline phosphatase)	X[2]				X[1]		
Attenuation scan		X			X		
^{18}F-fluoride PET scan		X			X[2,4]		
Torso survey		X			X		
Vital signs		X			X		
Concomitant medications	X		X			X	
Adverse event assessment	X	X	X		X	X	
Medical record review	X						

± Includes review of metastatic biopsy completed within 60 days of enrollment.

1. Physical exams, bone scans, CT/MRI(if MRI was indicated) scans, x-rays(if indicated), PSA, bone alkaline phosphatase, and uNTx are obtained within 60 days prior to enrollment and at following visits as a part of routine standard clinical care which will be collected and reviewed as part of this imaging trial. We will be assessing the results of these to compare to PET images. These tests are included and required in the therapeutic Febbo study. ACRIN will obtain data on these tests through a data sharing agreement.
2. Post-treatment PET imaging to be performed 12 weeks after treatment initiation (+/- 4 weeks to accommodate for scheduling in the research PET suite).
3. Dasatinib should be initiated within 7 days after pre-treatment PET imaging.
4. Should clinical progression (including disease progression, pain, etc.) occur prior to the 12-week imaging time point, the study leadership encourages the site PI to recommend completion of the second ^{18}F-fluoride PET scan prior to the participant going off study, if the participant is physically capable of completing the scan. However, this intermittent time point should occur only in those cases of clinical progression.

10.0 IMAGING PROTOCOL, ANALYSIS, AND SUBMISSION

10.1 Imaging Protocol

Participants with castration-resistant bone metastatic prostate cancer planning to receive dasatinib on a therapeutic clinical trial will undergo a PET scan, using ^{18}F-fluoride as a tracer to detect metastatic sites and evaluate normal bone, prior to treatment and again 12 weeks (+/- 4 weeks to accommodate for scheduling in the research PET suite) after initiation of dasatinib therapy, at each participating institutions' PET imaging suite.

The study will involve performance of 2 separate PET scans, a pre-treatment and post-treatment PET scan. Specifics for imaging procedures are available online in the study-specific Imaging Manual at www.acrin.org/6687_imagingmaterials.aspx. Updates to the Imaging Manual will be distributed via email to sites. Quality control measures will include confirmation of Imaging Manual version number on the Imaging Transmittal Worksheet (ITW).

10.2 Methods of Image Analysis

Twenty-four (24) patients with castrate (serum testosterone < 50 ng/dl) prostate cancer bone metastases enrolled to receive dasatinib on a separate phase 2 clinical trial (Febbo protocol) will be evaluated in this companion imaging biomarker study. Each patient will first undergo procedures as per the separate Febbo protocol. This will first entail an image-guided biopsy of a prostate cancer metastasis to determine whether the patient has an "AR high" or an "AR low" (Src signature which is the inverse of AR high) DNA microarray signature. This is in attempts to understand the biology of each individual's mechanism of castration-resistance. If the patient's tumor has an "AR high" signature, he will first receive treatment with nilutamide (Arm A). If an "AR low" (Src signature) pattern is identified, the patient will receive treatment with dasatinib (Arm B). At the time of progression, dasatinib will then be added to patients in Arm A and nilutamide to patients in Arm B. Only participants that are receiving dasatinib are eligible for this companion ^{18}F-fluoride PET imaging protocol (participants receiving nilutamide only will not undergo ^{18}F-fluoride PET imaging). This is regardless of whether they are on Arm A or Arm B, but they must be at a point in the therapeutic study where they are receiving dasatinib to be eligible.

Each participant will undergo ^{18}F-fluoride PET scanning prior to initiation of dasatinib therapy (baseline), and again 12 weeks after initiation of dasatinib. Our goal will be to accrue 12 patients to Arm A and another 12 patients to Arm B. SUV and dynamic analysis, which allows us to estimate K_i and K_1 will be performed on the ^{18}F-fluoride PET studies (at sites of bone metastases and adjacent normal bone). These parameters will be compared individually in each patient to determine change in response to treatment from dasatinib. Additionally, these parameters will be compared to determine whether there are major differences between normal bone and bone metastases and whether treatment related changes are preferentially occurring in bone metastases over normal bone. All parameters will be compared directly to PSA (monthly), urine N-telopeptide (monthly), bone alkaline phosphatase (monthly), as well as chest/abdomen/pelvis CT scans and bone scans obtained both at baseline and at 12 weeks. The participants will be followed prospectively, while on the Febbo therapeutic study, to determine time to bone metastatic disease progression and time to skeletal-related events (SREs). Coordinator assessments for progression and SRE endpoints will occur once every 3 months. Skeletal-related events will be defined as a pathologic bone fracture, confirmed by x-ray, CT, or MRI, surgery to bone, radiation to bone, or a spinal cord compression, confirmed by CT or MRI.

PET image analysis will be performed by the following methods:

- SUV quantification measures the total concentration of the radioactive label at any given time. A full body sweep will be performed.

  $$SUV = \frac{\text{decay corrected maximal region of interest activity (mCi/mL)}}{\text{Injected dose (mCi)/body wt (g)}}$$

- Compartmental or graphical analysis of dynamic scans – The dynamic imaging field will be selected to include the most prominent site of bony metastasis at the discretion of the local imaging team, with preference to those regions that include the heart or a major blood vessel. A fixed-size region of interest will encompass the area of maximum uptake on the summed dynamic images (30-60 minutes) in the metastasis, preferentially including the great vessels. Specific measures of interest include: K_i, an indicator of net plasma clearance of fluoride to bone mineral and K_1, an indicator of bone blood flow, and an indirect measure of angiogenesis.
- Local sites will estimate SUVs; however, all image analysis will be performed by the central ACRIN core laboratory.

10.4 Image Submission

For this protocol, the following images will be collected and submitted to ACRIN.

- Clinical CT and bone scans performed as part of standard of care;
- MRIs if performed as part of the bone metastasis evaluation;
- Any other scans performed as part of the bone metastasis evaluation, such as x-ray.

These protocol required images must be in DICOM format on CD/DVD-ROM or submitted via the internet using secure File Transfer Protocol (FTP), and transmitted along with an Imaging Transmittal Worksheet (ITW) which can be found on the ACRIN 6687 web site (www.acrin.org/6687_protocol.aspx).

The required images must be submitted to ACRIN Imaging Core Lab. ACRIN can provide electronic image submission and anonymity utilities for participating institutions via TRIAD software. For support in sending the images via the internet using TRIAD, contact the representatives of the Image Management Center (IMC) via email at Triad-Support@phila.acr.org or via phone: 215-940-8820.

10.4.1 If required and part of the protocol, images maintained at ACRIN Headquarters Image Archive may be distributed to other participating sites, using FTP, or CD-ROM where appropriate, for purposes of secondary review.

10.4.1.1 Removal of Confidential Participant Information: The header record on DICOM formatted image data, which often contains information identifying the participant by name, MUST be scrubbed before the image are transferred.

This involves **replacing** the following:

- Participant Name tag with the ACRIN Institution ID or number
- Participant ID tag with the ACRIN case number, and
- Other Participant ID tag with ACRIN Study Number.

10.4.1.2 FTP Transfer: Digitally generated image files in DICOM v3.0 format can be transmitted to the ACRIN IMC via FTP directly to the image archive. This

can be performed using a customized software program or by using TRIAD software available from ACRIN. An Imaging Transmittal Worksheet (ITW) must be faxed at the time images are transmitted. Contact the ACRIN IMC for additional details at Triad-Support@phila.acr.org

10.4.1.3 Please fax the ITW to:

ACRIN Core Lab at (215) 923-1737,
ATTN: ACRIN 6687 Imaging Specialist

10.4.1.4 In the event that the transfer of scrubbed image headers is not available, images may also be sent on a CD/DVD-ROM to the ACRIN IMC for transfer to the image archive. Please contact ACRIN prior to sending the media to confirm compatibility.

10.4.1.5 Images and the ITW may be mailed to:

American College of Radiology Imaging Network
MR/CT Core Laboratory
Attn: ACRIN 6687
1818 Market Street 16th floor
Philadelphia, PA 19103

11.0 ADVERSE EVENTS REPORTING

Adverse Event Reporting must follow the guidelines below. The ACRIN Adverse Event Reporting Manual [May 2008 version or latest revision—available on the ACRIN web site] provides additional details and may be consulted as a reference, but does not supersede AE reporting as specified in this protocol. The AdEERS electronic AE reporting system is to be used for AE reporting of AdEERS qualified events unless unavailable. AE data is to be entered into the AdEERS electronic system if it meets AdEERS criteria (see Section 11.8 and 11.9 for AdEERS reporting criteria), even when it has been manually captured and/or manually submitted due to system unavailability (see manual process below).

11.1 Definition of Adverse Event

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event (SAE)
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

11.2 Definition of Serious Adverse Event

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- results in death, or
- is life-threatening (at the time of the event), or
- requires inpatient hospitalization or prolongation of an existing hospitalization, or
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

11.3 Adverse Event Grading

Grade denotes the severity of the AE. An AE is graded using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, or the following categories (if the term does NOT appear in the current version of the CTCAE):

1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

(For terms listed in the CTCAEv4.0, the grade is still recorded as 1, 2, 3, 4, or 5; however, the definition of the various grades will be specific to the term being used.)

11.4 Adverse Event Attribution

Attribution determines whether an AE is related to a study treatment or procedure.

Attribution categories are:

Definite—AE ***is clearly related*** to the study treatment or procedure.
Probable—AE ***is likely related*** to the study treatment or procedure.
Possible—AE ***may be related*** to the study treatment or procedure.
Unlikely—AE ***is doubtfully related*** to the study treatment or procedure.
Unrelated—AE ***is clearly NOT related*** to the study treatment or procedure.

11.5 Potential Expected and Unexpected Adverse Events

AEs may be **expected** or **unexpected**:

- An **expected AE** is one that is described in the protocol, the ICF, or the investigator's clinical brochure.
- An **unexpected AE** is one that has not been described in the protocol, the ICF, or the investigator's clinical brochure.

11.6 Expected Adverse Events Associated With ^{18}F-Flouride PET Scans

11.6.1 Expected Adverse Events From PET or PET/CT Scan

- Discomfort;
- Claustrophobia.

11.6.2 Expected Adverse Events From ^{18}F-Flouride (IND # REMOVED)

Fluoride is a normal body constituent. The amount of fluoride ions in Sodium Fluoride F 18 Injection at the indicated dose is expected to have minimal effect on normal human physiology. When sodium fluoride F 18 Injection was approved for marketing in 1972, no adverse reactions were noted in over 400 patient studies reported in the medical literature [FDA, 2000]. In a 1999 review of the published literature, publicly available reference sources and adverse drug reaction reporting systems indicated that no adverse reactions have been reported for Sodium Fluoride F 18 Injection [FDA, 2000]. However, as with other injectable drug products, allergic reactions and anaphylaxis may occur.

- Minor allergic reaction (such as skin rash) is very unlikely, but can occur.

11.6.3 Expected Adverse Events From IV Needle Placement

- Hemorrhage (hematoma at the injection site);
- Infection (catheter related infection) at the injection site;
- Minor discomfort;
- Bleeding;
- Infection;
- Bruising.

11.6.4 Expected Adverse Events Associated With Radiation Risks

Radiation exposure is minimal. The radiation dose from the PET has not been shown to have any adverse effects. Whole body doses are 899 mrem from ^{18}F-fluoride. Additional exposure from attenuation imaging will be about 25 mrem for PET-only devices. If PET/CT devices are used, the total radiation exposure from ^{18}F-fluoride PET with CT totals 1360 mrem.

11.6.5 Adverse Events Related to Therapeutic Treatment

AEs related to therapeutic treatment will not be reported for this trial but reported to the Febbo trial investigators at the local institution. Only AEs that occur within 24 hours (± 4 hours [approximately 10 half lives]) of ^{18}F-fluoride administration will be reported, regardless of attribution/relatedness. Beyond this period, AEs that are determined to be definitely, probably, or possibly related to the subjects' underlying condition or therapy that are ALSO determined to be unrelated to the agents and procedures specified by this protocol, will not be reported, as the investigational agent is an imaging agent.

11.7 Reporting of Adverse Events

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 institutions should have

access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: http://ctep.cancer.gov/reporting/ctc.html. A list of AEs that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section 6 (Pharmaceutical Information).

Prompt reporting of AEs is the responsibility of each investigator, clinical research associate (RA), and/or nurse engaged in clinical research. Anyone uncertain about whether a particular AE should be reported should contact the ACRIN headquarters at 215-574-3150 for assistance. This study will be monitored by ACRIN and by the NCI's Cancer Imaging Program (NCI/CIP).

All AEs should be followed by the investigator until the events are resolved, the subject is lost to follow-up, the condition is stabilized, or the AEs are otherwise explained. Any death or any AE (e.g. development of cancer, congenital anomaly in conceived offspring) that is determined to be possibly, probably, or definitely related to study agents or procedures as specified in this protocol—even if it occurs after a subject has discontinued study participation—must be reported to the ACRIN AE Coordinator at DMC and to all appropriate study monitors and applicable regulatory authorities as specified herein or as required by regulation or guidance.

Assignment of grades and attribution for each AE/SAE must be completed by the site principal investigator or investigator-designee. All AEs/SAEs must be documented in the participant's study chart, AE form, and events that qualify for AdEERS must be submitted through the electronic-AdEERS (e-AdEERS) system in the required timeframes, as specified below. The ACRIN RA will capture all AEs as required herein on the AE form and in the e-AdEERS system where appropriate. This will ensure that they are provided to the NCI/CIP Monitor and will also ensure their receipt by the AE Coordinator at the DMC. Expedited AdEERS reports must be entered by the investigator or investigator-designee. The expedited AdEERS report will be submitted to the lead group reviewer at ACRIN and then submitted once reviewed to the NCI/CIP. A copy of the report must be kept on file at the site. Significant new information on any on-going AE/SAE should be promptly reported to NCI/CIP and ACRIN.

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must elicit, through open ended questioning (e.g. "How are you feeling?") information on AEs and, if indicated, the subject should be evaluated clinically. Information on all serious and non-serious, expected and unexpected AEs considered unrelated, unlikely, possibly, probably, or definitely related to ^{18}F-fluoride that occur within 24 hours (± 4 hours [approximately 10 half lives]) of ^{18}F-fluoride administration with the severity level of grades 1, 2, 3, 4, and 5 should be recorded immediately into the source document (e.g. ACRIN AE Log and/or progress notes of the participant's study chart) and retained at the site. These AEs will also be recorded in the AE form and entered into the e-AdEERS system as required, pending review by the principal site investigator in real time to determine grade and attribution of the event and timeframe for submission to ACRIN.

All SAEs that are still ongoing at the end of the study must be followed up to determine, to the degree possible, the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study procedures or study participation should be recorded and reported immediately.

11.8 E-AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 24 Hours (± 4 Hours) of a Dose of the Investigational Agent: ^{18}F-fluoride

Table 3. Reporting Requirements for Adverse Events That Occur Within 24 Hours (± 4 Hours) of a Dose of the Investigational Agent (^{18}F-fluoride)[1]

	Grade 1	Grade 2		Grade 3				Grades 4 & 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

11.8.1 Expedited AE Reporting Timelines

- **24 Hours; 5 calendar days** – The ACRIN investigator or investigator-designee must initially report the AE via e-AdEERS within 24 hours of first knowledge of the event followed by a complete e-AdEERS report within 5 calendar days of the initial 24-hour report.
- **10 calendar days** – A complete e-AdEERS report on the AE must be submitted within 10 calendar days of the ACRIN investigator or investigator-designee's first knowledge of the event.
  - Any medical event equivalent to CTCAE version 4.0 grade 3, 4, or 5 that precipitates **hospitalization* (or prolongation of existing hospitalization)** must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
  - Any event with an IND imaging agent–related attribution of **possible, probable,** or **definite** that results in **persistent or significant disability/incapacity, congenital anomaly, or birth defect** must be reported via e-AdEERS by ACRIN if the event occurs following treatment with an agent under a CIP IND.
  - Expedited reporting is defined as immediate notification to ACRIN and NCI/CIP through submission of an e-AdEERS report. Some AEs require 24-hour

notification via e-AdEERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to the CIP monitoring service, as specified below, by telephone. Routine reporting requirements also apply.

11.9 How to Report

NOTE: The e-AdEERS system routes AE reports to the necessary recipients/reviewers. The following contact information is provided to indicate the per-protocol recipients, forwarding timeframes, and distribution in the event this process must be done manually:

11.9.1 Some AEs require 24-hour notification (refer to Table 3 in Section 12.8) via e-AdEERS. When Internet connectivity is disrupted, a 24-hour notification is to be made as follows:

- Fax AE submission form and any additional information[1] necessary for thorough review of the event(s) to 301-897-7402, attention CIP SAE Team. The phone number for the CIP SAE Reporting Desk is 301-897-1704.

- Follow up with an e-mail to CIPSAEReporting@tech-res.com notifying that an AE form and additional information (if available) has been faxed.

Once Internet connectivity is restored, a 24-hour notification that was faxed or phoned in must be entered electronically into AdEERS by the original submitter at the site.

When the AE requires expedited reporting, submit the report within the number of calendar days of first knowledge of the event specified in Table 3 in Section 12.8. An expedited AE report requires submission to NCI by the DMC via the e-AdEERS system. CIP will then be notified via e-AdEERS and ACRIN of the expedited reporting. An expedited e-AdEERS report will be submitted to the lead group reviewer at ACRIN and then submitted once reviewed to the NCI/CIP.

11.9.2 Recipients of e-AdEERS Reports:

e-AdEERS Reports are electronically submitted to the following trial personnel; in the event that Internet connectivity is disrupted, AdEERS reports should be submitted as in Section 12.9.1 (above) and faxed to the attention of:

To ACRIN:
Maria Oh: moh@acr-arrs.org
Attention: ACRIN SAE Coordinator
Cornelia Tsikos: ctsikos@acr-arrs.org
RE: Adverse Event Report
ACRIN Protocol 6687
1818 Market Street
Suite 1600
Philadelphia, PA 19103

[1] For events unrelated to the imaging intervention, no additional information is necessary. For events possibly, probably, or definitely related to the imaging intervention, additional information should include, admission and discharge summaries (when available), laboratory workup, progress notes, circumstances of the event(s).

CIP SAE Reporting Desk:
Phone: 301-897-1704
Fax : 301-897-7402
Email: CIPSAEReporting@tech-res.com
ATTN: CIP Support S&P Manager, Anna Edouard, MD

11.9.3 All fatal AEs identified in the ^{18}F-fluoride PET scan component of the study must be reported by telephone within 24-hours of first knowledge of the event. To make a telephone report, call ACRIN at **215-717-2763**, available 24 hours a day (recorder after hours Monday through Friday from 4:30 PM to 8:30 AM Eastern Time and on weekends).

11.9.4 All fatal AEs identified in the ^{18}F-fluoride PET scan component of the study must also be reported to CIP by telephone at **301-496-0737** within 24-hours of first knowledge of the event and via e-AdEERS.

11.9.5 All expedited AE reports should be sent to the local Institutional Review Board (IRB). Refer to the IRB policies and procedures for AE reporting.

11.9.6 For automated CDUS reporting for studies using investigational agents, the DMC routinely reports AEs electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The DMC submits this data quarterly. The AEs reported through AdEERS will also be included with the quarterly CDUS data submissions.

Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

12.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference of Harmonisation [ICH] guidelines), applicable government regulations, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB) for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to ACRIN before implementation of the study.

The investigator will provide ACRIN with the institution's federal wide assurance (FWA) number, along with the IRB approval letter and copy of the IRB-approved ICF. The investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

All study participants in this study will be given an IRB-approved, site-specific ICF describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix I for an ICF template). The ICF will be submitted along with

the protocol for review and approval by the EC/IRB. The study participant MUST be consented with the EC/IRB-approved ICF before the participant is subjected to any study procedures. The approved ICF MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent. Any revisions to the ICF at any time during the trial will need to be submitted to the IRB for approval and submission to ACRIN PDRC.

13.0 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with ACRIN Conflict of Interest policies and applicable federal, state, and local laws and regulations.

14.0 PUBLICATION POLICY

Neither complete nor any part of the results of the study obtained under this protocol, nor any information provided to the investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of ACRIN, the Study Chairs, and/or the ACRIN Publication Committee. Any investigator involved in this study is obligated to provide ACRIN with complete test results and all clinical data obtained from the participants in this protocol. Investigators will follow the ACRIN Publication Policy (available online at www.acrin.org/PublicationsPolicy.aspx).

15.0 INSTITUTIONAL MONITORING AND AUDITS

The investigator will permit study-related auditing and inspections of all study-related documents by the EC/IRB, government regulatory agencies, and ACRIN. The investigator will ensure the capability for inspection of all participating sites' study-related facilities (e.g. imaging centers, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits.

Oversight for this study at all sites will be provided by the investigator with delegation of appropriate responsibilities to sub-investigators and designated study personnel. They will ensure all entry criteria are met prior to the initiation of the protocol and all study procedures and reporting of adverse events are performed according to the IRB-approved protocol.

15.1 Monitoring

Monitoring ensures that the rights, safety and well-being of the participants are protected. Monitoring also makes certain that the trial is in compliance with the currently approved protocol/amendments, with GCP and applicable regulatory requirements. It will provide the site an opportunity to verify that reported trial data are accurate, complete and verifiable from source documents. Institutional monitoring will be implemented at several different time points during the conduct of the study.

Monitoring instructions will be sent to the site prior to the implementation of monitoring to aid in preparation for the review. The instructions will specify regulatory documents and participant case records scheduled to be monitored. Case report forms (CRFs) and source documents of selected study participants enrolled at each site will be reviewed. In addition, the initial regulatory documents and any revised regulatory documents will also be monitored.

15.2 Audits

All participating institutions that enroll participants will be audited. The timing of the initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site-specific), the number of evaluable participants enrolled at an individual site, the status of the protocol and pending amendments, and monitoring status. Generally, audits will be conducted after the number of evaluable participants reaches 20% of targeted accrual, either study-wide and/or site-specific. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate immediate auditing. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited. Additionally, site-specific circumstances may prompt an audit at any time.

Subsequent audits will be scheduled per the outcome of the initial audit. Audits can be conducted more frequently at the discretion of the protocol team. The audits will be conducted per procedures established by the Cancer Imaging Program (CIP) of the NCI. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. These instructions will specify which participant case records will be reviewed during the audit. On-site records will be verified against the submitted form, and the findings will be recorded on specially-prepared audit reports. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and ICFs will also be reviewed at the time of the audit visit. The ACRIN Audit Manual is available online at www.acrin.org/pdrc.aspx.

To help sites prepare for monitoring and audits and to assure that the investigator and the research staff maintain records appropriately, ACRIN Headquarters will offer training to sites. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial.

15.3 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ACRIN.

Source documents must verify the eligibility criteria and data submitted on all CRFs. If an item is not mentioned (e.g., history and physical examination alluding to a condition, but no mention of a psychological condition), it will be assumed it is not present.

Research records for each case should contain copies of the source documents for the data collected and reported to ACRIN. If data are abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. Every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol. This will prevent any discrepancies and the inability to verify the document and the data reported.

15.4 Case Report Forms (CRFs)

CRFs, both web-based and paper forms, are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank on paper CRFs because the procedure was not done or the question was not asked, "N/D" must be noted. If the item is not applicable to the individual case, "N/A" must be noted. All entries on paper CRFs must be printed legibly in black ink on the paper CRFs. In the event of any entry errors, corrections must be made by drawing a **single straight line** through the incorrect entry, writing **the initials of the person making the correction, recording the date** when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser. Please refer to ICH Good Clinical Practice Guidelines.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be reviewed against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires must be available for review. Required study image interpretation data that are more detailed in information than the image and not typically documented in the standard radiology report may be documented on the CRF and are acceptable source documentation **if signed by the Investigator**. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date of the exam(s) from the medical record(s). Any use of approved CRFs as source documentation require a signature and date on the CRF with a reference to the information source (participant questionnaire, CT, MR, etc.). Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a major protocol deficiency.

Follow up for the ACRIN trial will comprise data transfer of a subset of Febbo trail follow-up data for the ACRIN cohort of participants.

15.5 Institutional Review Board

Sites must obtain initial local IRB approval to participate in ACRIN trials. Prior to participant registration, a copy of the IRB approval letter for the protocol and the ICF must be sent to ACRIN, along with a copy of the IRB-approved, site-specific ICF. Investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

16.0 STATISTICAL CONSIDERATIONS

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APPENDIX I

INFORMED CONSENT FORM TEMPLATE

ACRIN 6687

A Phase 2, Multicenter Evaluation of ^{18}F-Fluoride PET as a Pharmacodynamic Biomarker for Dasatinib, a Src Kinase Inhibitor, in Men With Castration-Resistant Prostate Cancer and Bone Metastases (BMS #180-279)

[Note: The American College of Radiology Imaging Network (ACRIN) does not monitor compliance with the Health Insurance Portability and Accountability Act (HIPAA); that is the responsibility of local Institutional Review Boards (IRBs). Local IRBs may choose to combine the authorization elements in the informed consent. Information on ACRIN's HIPAA policy, as well as a template for HIPAA authorization, can be found at www.acrin.org.]

This is a clinical trial, a type of research study. Your study doctor will explain this clinical trial to you. Clinical trials include only participants who choose to take part. Please take your time with your decision to take part. You are encouraged to discuss all parts of this study with your family and friends and to ask your healthcare team as many questions as needed.

If you want more information about participating in clinical trials, ask your study doctor for the National Cancer Institute (NCI) booklet *Taking Part in Cancer Research Studies*. Also, you can learn more about clinical trials at http://cancertrials.nci.nih.gov or by calling the NCI's help line at 1-800-4-CANCER (1-800-422-6237 or TTY: 1-800-332-8615).

You are being asked to be in this study because you have been diagnosed with prostate cancer and you are receiving treatment with dasatinib on the Febbo study called—"Genomic Guided Therapy with Dasatinib or Nilutamide in Metastatic Castration-Resistant Prostate Cancer". This study is an addition to the Febbo study to try to see how the dasatinib therapy affects the body. Another treatment, called nilutamide, also is being examined in the Febbo trial. If you receive nilutamide only during the Febbo trial, you will not undergo the ACRIN 6687 imaging part of the study.

This study will also be using positron emission tomography (PET) scans with an investigational imaging agent that the Food and Drug Administration (FDA) is studying. If you decide to volunteer for this study, you will be asked to sign and date this form.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to measure changes in prostate cancer that has spread to a bone and also to evaluate changes in normal bone for patients receiving treatment with dasatinib. Images will be made of injected compounds labeled with small amounts of an investigational radioactive substance, also called radioactive drugs or "tracers." This is a procedure called positron emission tomography (PET). The investigational radioactive tracer used in this study called ^{18}F-fluoride has been used for imaging bones in patients with many other diseases. This study is testing to see how useful ^{18}F-fluoride PET exams are

for evaluating prostate cancer in bone as well as normal bone. To see if these images might be useful, they will be studied and compared to standard prostate cancer blood, urine, and imaging tests.

The use of ^{18}F-fluoride for prostate cancer is experimental and is not approved yet by the FDA for routine use in people diagnosed with prostate cancer. Because it is experimental, the results will not be used in planning your regular care. There is increasing evidence; however, that these PET scans may be useful in certain situations. This trial's results will add to the evidence available on this agent as the FDA decides whether it should be used regularly to help people with prostate cancer.

About PET Scans

PET is a nuclear medicine imaging technique that produces a 3-D image of how the body functions. In other words, PET scans take pictures of the cells and how they work in the body—in this case, in the bones.

About the Radiopharmaceutical ^{18}F-fluoride

The ^{18}F-fluoride agent is investigational radiopharmaceutical, a molecule containing radioactive substance. The agent builds up inside the bone and can be seen on PET scan images. The images show color where the ^{18}F-fluoride emits radiation so doctors can see the tumor.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 24 people with prostate cancer and being treated with dasatinib from the Febbo therapeutic study titled "Genomic Guided Therapy with Dasatinib or Nilutamide in Metastatic Castration-Resistant Prostate Cancer" will take part in this study.

You may or may not receive the dasatinib in the Febbo trial. If you do not, you will not have to complete the imaging for this trial even though you agree now to have it done. Patients receiving nilutamide only during the Febbo trial will not undergo ^{18}F-fluoride PET imaging.

HOW LONG WILL I BE IN THE STUDY?

You will be directly involved with this clinical trial's imaging procedures for about 16 to 18 weeks after you are enrolled to participate. This will depend on when you are able to have your study procedures scheduled for this study. Each imaging day visit will require about two (2) to three (3) hours of your time.

In addition, research staff will work with your treating physician to review and collect information such as your medical history, pathology reports and specimens, radiology reports and films, radiotherapy treatment records, hormone treatment records, chemotherapy treatment records, results of laboratory studies, and all medications. We will be collecting this information for up to 5 years, to compare the results of the PET scan with the course of your cancer. The ^{18}F-fluoride PET scans in this study will be taken as you undergo different stages of treatment for your prostate tumor.

This study is expected to end after all study participants have completed the imaging visits and all the information has been collected. This study may be stopped at any time by your study doctor, ACRIN, FDA, and/or NCI without your consent should:

- Your health or safety be at risk;
- You not follow study instructions;
- The study drug no longer be available;
- New information becomes available that might change your mind about participating in the trial;
- An administrative decision made by the study doctor, ACRIN, FDA, and/or NCI.

These actions do not require your consent, but you will be informed of any of these decisions if such a decision is made.

You can stop participating in this study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your family doctor first. Withdrawal will not interfere with your future care. There will be no penalty for deciding not to participate.

WHAT AM I BEING ASKED TO DO IN THE STUDY?

If you agree to take part in this study, you will have the following tests and procedures. See the Study Chart at the end of this section for a visit-by-visit outline of what will be expected of you if you decide to participate in this trial.

Standard medical procedures that are part of regular cancer care and would probably be done even if you do not join the study:

- Medical history, records, and reports review;
- CT and/or MRI scan;
- Bone scan;
- Other scans, like x-rays;
- Urine test for N-telopeptide;
- Physical examination;
- Blood tests for bone alkaline phosphatase;
- Prostate specific antigen (PSA).

Medical procedures that are being done specifically as part of the Febbo therapeutic study titled "Genomic Guided Therapy with Dasatinib or Nilutamide in Metastatic Castration-Resistant Prostate Cancer":

- Bone biopsy;
- Cancer fighting drug called dasatinib.

Medical procedures that are being done specifically because you are in this study (these may or may not be done if you were not in this study):

- Two (2) PET scans with ^{18}F-fluoride.

Before treatment. You will be asked to have one (1) ^{18}F-fluoride PET scan within 7 days prior to starting treatment with dasatinib for your prostate cancer.

During treatment. After you start treatment, you will have one (1) ^{18}F-fluoride PET scan approximately 12 weeks after you have started your treatment with dasatinib.

Intravenous (IV) catheters. Each visit when you have the ^{18}F-fluoride PET scan, you will need to have an IV catheter placed in a vein of your forearm or hand to inject the investigational radiopharmaceutical ^{18}F-fluoride for the PET scan. The IV is necessary for injection of a small amount (10 ml, about two teaspoons) of the ^{18}F-fluoride.

The PET study data collection begins immediately after injection of the radioactive tracer and continues for about an hour. The ^{18}F-fluoride will travel to your bones to aid in the images created by the PET scanner. The catheter will be removed at the end of the PET scan.

Preparation for a PET scan. Before each ^{18}F-fluoride PET scan, do not eat for 4 to 6 hours before your appointment time, and drink only water. You will be given details of what to do to prepare for your PET scan.

During the PET exam. Each day of your ^{18}F-fluoride PET scan, you first will be given an injection of a small amount of the^{18}F-fluoride into a vein of your forearm or hand. The amount of radiation is small, comparable to x-ray studies like CT. The radioactive tracer only stays in your body for a few hours. It is passed when you go to the bathroom through urine.

You will be asked to drink large amounts of water before and after you are injected with ^{18}F-fluoride. You will also be asked to use the bathroom one-half hour before and after you have been injected with the investigational radioactive tracer. You will be provided with specific instructions at the time of your first visit.

The PET scanner is a large machine with a hole in the middle. It looks like a donut with a table in the middle. It contains crystals that pick up tiny radiation signals from the tracer (radioactive drug) in your body. It is able to determine the region of your body from which the radiation signals arise. With the help of computers, the signals are added up and portrayed as a map of the tracer in body organs or tumors.

After the injection of ^{18}F-fluoride, you will be asked to go to the bathroom (urinate) and then lie on a partially enclosed scanning table, face up. The size of the opening is 27 to 30 inches. How much space you feel you have around you will depend on your body size and the scanner type. If you feel any anxiety over being in enclosed spaces, let your study doctor know. A mild sedative may be used to help you feel more comfortable during the exam.

The table will slide into the machine. You will be asked to remain still during the scan. To help you keep from moving, the PET staff will help you get comfortable, then hold you in place with wide straps across your chest and abdomen. You will hear buzzing or clicking sounds during the scan. You will lie on a comfortable table for about 90 to 120 minutes. You will be scanned from your feet to your head. The scanning takes about three-fourths of the visit; the other fourth is used for setting up, positioning,

etc. After the scanning has been completed, you will need to lie still for about 20 minutes before coming off of the scanning table.

Time required. The entire ^{18}F-fluoride PET scan procedure is expected to take no more than 4 hours from the time of the ^{18}F-fluoride injection. Because you will need to lie still for about 90 to 120 minutes, you may need to wear a condom-style catheter. This will allow you to urinate during the PET procedure if you need to.

Follow up. You will continue to see your treating doctor at regular intervals according to her/his recommendations and usual practice. Information gathered by your treating doctor as part of your normal follow-up visits will be given to your study doctor(s) so they can find out more about your health.

Your treating doctor will be asked to inform the study's researchers about your health and your disease status for approximately for 5 years. Your follow-up care will be decided between you and your treating doctor.

AN OUTLINE OF THE STUDY FOLLOWS IN THE "STUDY CHART".

STUDY CHART

VISIT 1: Eligibility/Registration	• Sign this informed consent form (ICF); • Have a physical examination; • Provide medical history.
VISIT 2: Pre-Treatment ^{18}F-Fluoride PET Scan - Within 7 Days Prior to Treatment Initiation With Dasatinib	• Follow instructions provided at Visit 1: Eligibility/Registration in preparation for your 1st ^{18}F-fluoride PET scans; • Have vital signs taken; • Have IV catheter placed in a vein of your forearm or hand. • Have the ^{18}F-fluoride injected; • Have an^{18}F-fluoride PET scan.
VISIT 3: Telephone Contact – After 24-Hour Period After ^{18}F-Fluoride PET Scan	• Speak with your research nurse or staff and let them know how you are feeling.
VISIT 4: Post-Treatment ^{18}F-Fluoride PET Scan – Approximately 12 Weeks After Treatment with Dasatinib*	• Follow instructions provided at Visit 2 for your 1st ^{18}F-fluoride PET scans; • Have vital signs taken; • Have IV catheter placed in a vein of your forearm or hand. • Have the ^{18}F-fluoride injected; • Have an ^{18}F-fluoride PET scan.
VISIT 5: Telephone Contact – After 24-Hour Period After ^{18}F-Fluoride PET Scan	• Speak with your research nurse or staff and let them know how you are feeling.
FOLLOW UP: Every 2 Months for Up to 5 Years	• Every 2 months after you complete the therapeutic study your overall survival status will be assessed as part of that study. These data will be shared with the researchers for this imaging study for up to 5 years.

* In the event that you stop taking the dasatinib before you take it for 12 weeks, your study doctor may ask you to undergo the post-treatment PET scan earlier than after 12 weeks.

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS OF THE STUDY?

While on the study, you may be at risk for side effects. You should discuss the possible side effects listed below with the research staff and/or your treating doctor. There also may be other side effects that we cannot predict. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the imaging scan is stopped and IV catheters are removed, but in some cases, side effects can be serious, long lasting, or permanent.

If you receive Ativan or another sedative, there is a small risk of a reaction to the sedative medication. We will not administer this drug if you have had a bad reaction to similar medications in the past or if your medical history suggests that you are at risk for a reaction.

Risks Associated With Intravenous (IV) Catheter Placement:

Likely:
- Minor discomfort;
- Pain in the injection site.

Less Likely:
- Bleeding;
- Infection;
- Bruising.

Risks Associated With PET Scans:

- Discomfort;
- Claustrophobia.

Risks Associated With the Radiopharmaceutical ^{18}F-fluoride:

In previously studied patients who receive the same dose as you would, there were no side effects reported nor did the patients complain of any as a direct result of the tests. But if you notice anything differently, please contact your study doctor(s) (contact number given below).

^{18}F-fluoride, when it is given in a few small doses, like those being used in this study, is not known to cause any problems for humans. As with any drug that are injected, there may be anticipated side effects such as:

Less likely, but serious
- Allergic reaction.

Very rare, but serious
- Death due to severe allergic reaction.

Radiation Risk

<<Each site may need to modify this section to quote the correct PET and CT dosimetry for its own PET scanners in accordance with its own institutional policies and procedures. The following language and dosing range is an example only.>>

For example:

There are some risks from the PET scans used to monitor your tumor status and your response to treatment. These scans will expose you to radiation. If you live in the US, you receive about 300 millirem of radiation each year. It comes from space and the earth around you. This is called "background radiation." A "millirem" (mrem) is a unit used to measure doses of radiation. The radiation dose to your whole body from each of your PET scans will range from about 540 (for PET only scanners) to 1360 mrem (for PET/CT scanners). This dose can vary from person to person. If you have 1500 mrem, your risk of harm might be as high as 1 in 1000. If you have more procedures that expose you to radiation, your risk will go up. Risks of harm may include getting a new cancer or changes in your genes. You may need to have other x-rays or scans for your care. Your doctors will explain the risks of the other x-rays or scans.

In previously studied patients we have not noticed any appreciable side effects nor did the patients complain of any as a direct result of the tests. But if you notice anything differently, please contact your study doctor(s) (contact number given below).

Risks Associated With Sedative

If you choose to take a sedative, there may be side effects, such as:

- Drowsiness;
- Fatigue;
- Disorientation; and/or
- Memory changes.

If you take a sedative, you will not be allowed to drive yourself home due to drowsiness. We will not give it to you if you have had a bad reaction to similar medicines in the past, or if your medical history suggests that you might have a reaction.

Reproductive Risk

If you are planning to father a baby during the course of the study, you cannot take part in this research study. We do not know the side effects on an unborn baby. Because the PET scan and the investigational radiopharmaceutical ^{18}F-fluoride may affect an unborn baby, you should not father a baby while on this study.

You and your doctor should discuss taking precautions. During the study, you need to take safety measures to prevent pregnancy by not having sex or by using two forms of medically-accepted methods of birth control, such as a diaphragm, cervical cap, condom, surgical sterility, and/or birth control pills. If your partner does become pregnant, you will need to tell your study doctor immediately.

Ask about counseling and more information about preventing pregnancy.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THE STUDY?

You will not benefit from your participation in this study, but the information obtained from your images may lead to new cancer imaging methods for the future. The future benefits of this study include gaining knowledge for prostate cancer patients:

(a) where in the body dasatinib is active;

(b) what type of patient might benefit the most from treatment with dasatinib;

(c) how doctors can best determine how well patients respond to treatment with dasatinib;

(d) how long dasatinib treatment might be beneficial; and

(e) when to change treatment.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO PARTICIPATE?

You can choose not to take part in this study. If you choose not to participate, you will still receive regular medical care (such as CT and bone scans), and you will not undergo any of the study procedures. You can also choose to just be on the dasatinib therapeutic clinical trial and not participate on this companion PET imaging study.

WHAT ABOUT PRIVACY?

Every attempt will be made by the study team to keep all the information collected in this study strictly private as required by law, including your personal information. We cannot guarantee absolute privacy. Records of your participation in this study, your progress, and images taken while on the study (such as the ^{18}F-fluoride PET scans, CT scans, and Bone scans) will be kept secure at this institution and in a computer file at ACRIN headquarters in Philadelphia, PA. All data sent to ACRIN over the Internet will be coded so that other people cannot read it. Your personal information may be disclosed if required by law.

You further understand that authorized representatives of ACRIN, the Center for Statistical Sciences at Brown University, the NCI, Bristol-Myers Squibb, the IRB of *<<Institution>>*, and other groups or organizations that have a role in this study will have access to and may copy both your medical and research records due to your participation in this study. This access is necessary to ensure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner that you cannot be identified.

The US Food and Drug Administration (FDA) also reserve the right to review study data which may contain identifying information. If your research record is reviewed by any of these groups, they may also need to review your entire medical record. All of the above mentioned groups or organizations are required to maintain confidentiality regarding your identity.

Your research records and images will be kept permanently on file at ACRIN and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number. The information that may be done with the information will not specifically help you. But, it might help people in the future who have cancer and other diseases.

WILL I HAVE TO PAY FOR ANYTHING?

Taking part in this study will not lead to added costs to you or your insurance company. Many of the tests and procedures performed as a part of this study are considered routine care for patients with prostate cancer and will be charged to your insurance company in the usual manner. This includes the clinic visits, lab tests (PSA, urinary N-telopeptide, etc.), bone scans, and CT scans.

You or your insurance company will not be charged for the following part of this research study:

- Two (2) PET scans with ^{18}F-fluoride;
- Anxiety or pain medication while in the PET scan.

You may be responsible for any co-payments and deductibles that are standard for your insurance coverage.

You will not be paid for taking part in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE STUDY?

It is important that you tell your study doctor, *<<insert name>>*, if you feel you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at *<<insert telephone number>>*.

In the case of medical emergency, injury, or illness during this study, emergency medical treatment is available but will be provided at the usual charge. You and/or your insurance will be responsible for the cost of the medical care of that illness or injury. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is voluntary. You may choose not to take part in the study. If you decide to take part in the study, you are free to leave the study at any time. No matter what decision you make, there will be no penalty and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still be treated at our institution, and your decision will not interfere with your future care.

If you withdraw from the study, no new data about you will be collected for study purposes unless the data concerns any side effect related to the study. If such side effect occurs, we may need to review your entire medical record to follow any possible long-term problems from the event.

During the study, we may find out more information that could be important to you. A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. This includes information that might cause you to change your mind about being in the study. If information becomes available from this or other studies that may affect your health, welfare, or willingness to stay in this study, we will tell you about it as soon as possible.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

(This section must be completed)

You can talk with your study doctor(s) about any questions or concerns you have about this study. Contact your study doctor *<<insert name>>* at *<<insert telephone number>>*.

This document explains your rights as a study participant. It you have any questions regarding your participation in this research study or you have any questions regarding your rights as a research participant, do not hesitate to speak with your study doctor or anyone listed below.

For additional information about your health or medical emergency, you may contact: *Usually the name of the local hospital information is provided and with instructions to study participants to inform the ER doctor of their participation in a clinical trial.*

Name	Telephone Number

For information about your rights as a research subject, you may contact *<<Institution Name>>* Institutional Review Board (a group of people who review the research to protect your rights):
(Provide the name of local IRB contact person)

Name	Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

You may also visit the NCI's web sites for comprehensive clinical trials information, http://cancertrials.nci.nih.gov. For cancer information from the NCI, visit http://cancernet.nci.nih.gov.. More information on PET scans can be found in the "Patients" section of the ACRIN web site: www.acrin.org. You or your doctor can print a description of PET scans from this web site.

ACKNOWLEDGEMENT

When you sign this document, you are agreeing to take part in this study. This means you have read all the above information, asked questions regarding your participation, and received answers that you understand to all your questions. You have also had the opportunity to take this consent form home for review or discussion if you want to.

You willingly give your consent to participate in this study. A copy of this signed informed consent form will be given to you.

Printed Name of Study Participant/ Legal Representative	Signature	Date

<Insert other signature and date lines as appropriate per local IRB policies and procedures>

APPENDIX II

SUPPLEMENTAL MATERIALS AVAILABLE ONLINE

Supplemental materials that support the conduct of the trial are available on the ACRIN web site at the ACRIN 6687 Protocol web page (www.acrin.org/6687_protocol.aspx). Types of materials posted include:

- Application and protocol activation documents (General Qualifying and Protocol Specific Applications, FDA Form 1572, protocol activation checklist, etc.);
- Data forms;
- Imaging materials (Image Transmittal Worksheet, imaging parameter charts, and scanning and image qualification instructions);
- Recruitment and education materials;
- Regulatory resources;
- Participating site list.

For more information related to the trial, contact the ACRIN 6687 Contact Personnel link on the above-mentioned web page for a list of protocol team members at ACRIN Headquarters and their roles.