Evaluation of monosodium glutamate (MSG) to reduce salivary gland and renal accumulation of PSMA-binding radiopharmaceuticals

A sub-study of REB protocol H16-01551 ([^{18}F]-DCFPyL Positron Emission Tomography / Computed Tomography (PET/CT) for Assessment of Recurrent Prostate Cancer")

RESEARCH ETHICS BOARD PROTOCOL NUMBER: H18-02227

Principal Investigator: François Bénard, MD

Co-Investigators: Don Wilson, MD

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FUNCTIONAL IMAGING DEPARTMENT

BC CANCER - VANCOUVER

Sponsor Signature Page

François Bénard, MD Date

Sponsor (Lead Study Investigator)

Protocol Signature Page

Principal Investigator (Print Name)

Principal Investigator (Signature) **Date**

The above signed confirms herewith to have read and understood this study protocol, and furthermore, to accomplish this study according to the Protocol and the Good Clinical Practice guidelines, as well as local regulations, and to accept respective revisions conducted by authorized representatives

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1. List of Abbreviations

ACRIN	American College of Radiology Imaging Network
AE	Adverse Event
^{225}Ac	Actinium-225
BC	British Columbia
cm	Centimeter
CRF	Case Report Form
CRPC	Castration resistant prostate cancer
CT	Computed Tomography
CTA	Clinical Trial Application
ECOG	Eastern Cooperative Oncology Group
EuK	Glutamate-urea-Lysine
^{18}F-DCFPyL	2-(3-(1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid
^{18}F	Fluorine-18
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
%ID/g	Percent injected dose per gram of tissue
IV	Intravenous
^{177}Lu	Lutetium-177
MBq	Mega Becquerel
mL	Milliliter
mm	millimetre
MRI	Magnetic Resonance Imaging
MSG	Monosodium Glutamate
mSv	Millisievert
ng/mL	nanogram per milliliter
PBS	Phosphate-buffered saline
PET	Positron Emission Tomography
PMPA	(Phosphonomethyl) pentanedioic acid
PSA	Prostate Specific Antigen
PSMA	Prostate Specific Membrane Antigen
REB	Research Ethics Board
SAE	Serious Adverse Event
SPECT	Single Photon Emission Computed Tomography
SUV	Standardized uptake value
w/v	weight/volume

2. Protocol Synopsis

STUDY OBJECTIVES Primary: Secondary:	To evaluate the effects of orally administered monosodium glutamate (MSG) on salivary gland accumulation of [^{18}F]-DCFPyL. • To evaluate the effects of MSG on renal accumulation of [^{18}F]-DCFPyL. • To evaluate the effects of MSG on tumour accumulation of [^{18}F]-DCFPyL. • To evaluate the tolerability and compliance with an orally administered solution of MSG
STUDY DESIGN	This is a prospective single blinded intra-participant study to evaluate the effects of orally administered MSG vs placebo on ^{18}F-DCFPyL PET/CT biodistribution.
STUDY POPULATION Number of Participants: Age: Study specific requirements:	 10 participants. Age greater than or equal to 19 years Participants who are eligible to participate in protocol H16-01551 entitled '[^{18}F]-DCFPyL Positron Emission Tomography / Computed Tomography (PET/CT) for Assessment of Recurrent Prostate Cancer.'
INVESTIGATIONAL PRODUCT Product Route of administration: Dosage(s) and frequency: Duration of dosing:	 [^{18}F]-DCFPyL Intravenous Radioactive dose of [^{18}F]-DCFPyL: 296-521 MBq per injection Two injections per participant (two PET/CT scans) Single dose for each PET/CT scan
EVALUATION CRITERIA Efficacy: Safety:	 Salivary gland and renal accumulation of [^{18}F]-DCFPyL measured by the standardized uptake value. Vital signs before MSG administration, immediately before [^{18}F]-DCFPyL administration, 5-15 minutes following [^{18}F]-DCFPyL administration, 1 and 2 hours after [^{18}F]-DCFPyL administration; Adverse event collection.

3. Background Information

3.1. PSMA PET/CT imaging

The prostate-specific membrane antigen (PSMA) is a cell surface transmembrane glycoprotein that is significantly overexpressed in prostate cancers (1). It is also expressed in lower amounts in normal tissues such as the liver, gastrointestinal track and kidneys, as well as the vascular endothelium of some non-prostatic tumours (eg. breast, renal, lung) (2).

Several inhibitors of PSMA have been developed over the years, with the aim of blocking the enzymatic function of this protein. PSMA has multiple names, including glutamate carboxypeptidase II (GCPII), folate hydrolase I (FOLH1), and N-acetyl-L-aspartyl-L-glutamate peptidase I (NAALADase).

Due to high overexpression of PSMA in prostate cancer, there has been long term interest in targeting this protein to deliver radioisotopes to prostate cancer cells by using PSMA-binding molecules as a carrier. Most investigators have focused on the use of radiolabeled antibodies (notably the J591 antibody) or peptidomimetics derived from the glutamate-urea-lysine (EuK) sequence, to develop single positron emission computed tomography (SPECT) and positron emission tomography (PET) radiotracers.

Many radiopharmaceuticals showing high sensitivity/specificity for PSMA-expressing tissues have been developed, and the use of PSMA imaging is rapidly growing worldwide (3). While there is extensive experience reported in retrospective studies with [^{68}Ga]-HBED-PSMA-11 (4, 5), new radiopharmaceuticals labeled with fluorine-18, such as [^{18}F]-PSMA-1007(6) and [^{18}F]-DCFPyL (7-9) are rapidly gaining in popularity due to their advantages over ^{68}Ga-labelled compounds.

3.2. Radioligand therapy of prostate cancer

PSMA radiopharmaceuticals derived from the EuK backbone are also showing promise as a treatment for castration-resistant metastatic prostate cancer (10-12). In this application, the diagnostic radioisotope is changed for a beta (^{177}Lu) or alpha (^{225}Ac) emitter which induces radiation damage to cancer cells that bind the radiotracer, as well as surrounding cells. With both radioisotopes, the activity administered to patients is limited by toxicity to normal organs. Due to high accumulation in the kidney and salivary glands (13), potential side effects include renal dysfunction and xerostomia (10-12). Marrow toxicity may also occur (14), but this effect is probably related to indirect exposure from bone metastases in patients with extensive osseous

involvement. Xerostomia is more cumbersome with alpha-emitters, causing patients to discontinue treatment (15).

With radioligand therapy using ^{177}Lu-PSMA-617, in an Australian phase II study (12), where 4 cycles of treatment were administered, 87% of patients developed xerostomia. Most cases of xerostomia were mild (grade 1), and controlled with no treatment or salivary substitution gels. 17% of patients experienced dry eyes with recovery over time.

With ^{177}Lu-PSMA-617, Delker et al. reported absorbed doses per cycle of 0.6 Gy/GBq, 1.4 Gy/GBq, 0.1 Gy/GBq, 0.1 Gy/GBq and 0.012 Gy/GBq for the kidneys, salivary glands, liver, spleen and bone marrow, respectively (16). Kratochwil reported doses to the kidney of 0.75 Gy/GBq, red marrow of 0.03 Gy/GBq, and salivary gland of 1.4 Gy/GBq (17). Yadav et al. measured 1.24 ± 0.26 and 0.99 ± 0.31 Gy/GBq, for the salivary glands and kidneys, with a mean absorbed doses to the liver, urinary bladder and red marrow were 0.36 ± 0.10, 0.243 ± 0.09 and 0.048 ± 0.05 Gy/GBq, respectively (18). Kabasakal reported doses to the salivary glands, kidney and marrow at 1.17 ± 0.31 Gy/GBq 0.88 ± 0.40 Gy/GBq and 0.03 ± 0.01 Gy/GBq respectively (19).

Thus, the critical organs with EuK PSMA radiopharmaceuticals are the salivary gland and kidneys. The marrow is probably mainly affected when there is extensive metastatic infiltration of the bones. A means of decreasing radiation exposure to normal organs without affecting tumour uptake would allow administration of higher amounts of radioactivity with presumably greater anti-tumour effects.

3.3. Pharmacological approaches for salivary gland and renal protection

Different pharmaceuticals including 2-(phosphonomethyl)pentanedioic acid (PMPA), a PSMA inhibitor, have been explored for nephroprotection (20, 21). PMPA displaced renal activity of a PSMA radiotherapeutic in cancer models, but this was generally accompanied by a reduction in tumour uptake (20, 21). Mannitol infusion reduced renal uptake of 68Ga-PSMA-11 (22). Its effect on tumour uptake requires further investigations. Botulinum toxin administered in the parotid gland of a patient significantly decreased PSMA-ligand uptake (23). While this procedure is promising, it is invasive, costly, and may affect salivary gland function for weeks.

While PSMA is expressed to low levels in salivary glands and kidneys, part of PSMA-ligand uptake in salivary glands may be due to off-target binding, as uptake is not observed in human studies with the radiolabeled J591 monoclonal antibody (24-26). RNA and protein expression is

relatively low in salivary glands according to the human protein atlas (27, 28), compared to the prostate gland, duodenum and kidneys, yet radiotracer accumulation is equivalent or higher. This led to the hypothesis that a large fraction of salivary gland accumulation of EuK ligands might be caused by mechanisms other than PSMA binding. As glutamate is one of the most potent stimulator of salivary flow (29), glutamate transporters and receptors (metabotropic glutamate receptors, umami taste receptor, others) are potential candidates to explain the non-specific binding of EuK ligands to salivary glands.

3.4. Monosodium glutamate to block non-specific accumulation of PSMA ligands

As many PSMA ligands integrate glutamate for binding to PSMA, we hypothesized that monosodium glutamate (MSG) could reduce non-specific accumulation in non-cancerous tissues. MSG is a well-studied taste enhancer and a potent stimulator of salivary flow (29, 30).

MSG was investigated to reduce uptake of ^{68}Ga-PSMA-11 in salivary glands and kidneys, in LNCaP tumour-bearing mice (31). The mice were injected intraperitoneally with MSG (657, 329, or 164 mg/kg), or phosphate-buffered saline (PBS) as a negative control. Fifteen minutes later, the mice were intravenously administered ^{68}Ga-PSMA-11 as a representative EuK radioligand. PET/CT imaging and biodistribution studies were performed one hour after radiotracer administration. Tumour uptake was not statistically different between groups: 657 mg/kg (8.42±1.40 %ID/g), 329 mg/kg (7.19±0.86), 164 mg/kg (8.20±2.44), PBS (8.67±1.97). Kidney uptake was significantly lower in the 657 mg/kg group (85.8±24.2 %ID/g) than in the 329 mg/kg (159±26.2), 164 mg/kg (211±27.4), and PBS groups (182±33.5); $p < 0.001$. Salivary gland uptake was lower in 657 mg/kg (3.72±2.12 %ID/g) and 329 mg/kg (5.74±0.62) groups compared with PBS group (10.04±2.52, with a p value less than 0.01). This study concluded MSG decreased salivary and kidney uptake of ^{68}Ga-PSMA-11 in a dose-dependent manner, while no difference in tumour uptake was observed.

Obviously, these represent large doses of MSG, and it is not known what doses are necessary to achieve similar effects in human participants. It is also not clear if the effects of MSG are related to saturation of low capacity PSMA binding sites, or due to blocking of [^{18}F]-DCFPyL to other targets, as MSG has a Ki of 0.9 mM against human PSMA, measured in LnCAP cells.

3.5. The safety of monosodium glutamate, a flavour-enhancing ingredient

Although MSG has been linked to headaches and “Chinese restaurant syndrome” (32), numerous studies have shown MSG to be very safe, and the causal relationship with headaches has been questioned (33). Based on a no adverse event limit of 3,200 mg/kg/day for

neurodevelopmental toxicity, the European Food Safety Authority recommended an acceptable daily intake of 30 mg/kg/day (34, 35). The LD50 for orally administered MSG in rats in mice is approximately 15-18 g/kg (equivalent to an oral dose of 1.05 – 1.26 kg in an average adult male) (36). The average daily intake of glutamate in food is 13 g per day (37).

Glutamate was administered intravenously at a rate of 30-40 mg/kg/hour, to a maximum infusion of 9.2 g of a solution comprised of pH 6 solution of L-glutamic acid 9.2 g, NaCl 0.8 g, in 500 mL of water, in a study on the benefits of glutamate infusion during cardiopulmonary bypass surgeries (38). Fernstrom administered a single oral dose of 12.7 g of MSG in humans without undesirable events, with return of plasma glutamate levels to baseline after 3 hours (39). Chevassus et al. administered 150 mg/kg orally to 18 healthy volunteers, with a 75g oral glucose load, to investigate the effects of glutamate on insulin secretion. One participant reported dizziness, gastric discomfort and nausea, while another reported headaches, all of which were resolved by the next day (40). Shimada administered doses of 150 mg/kg daily (approximately 12 g for an 80 kg man) to 32 healthy volunteers for 5 consecutive days. They noted an increase in systolic and diastolic blood pressure as well as headaches, but no effects on muscle sensitivity (41).

The MSG quantity required to achieve effective off-target blocking of EuK radiolabeled derivatives in humans is not known, as human physiology may differ. We know from the evaluation of numerous EuK radiotracers in the preclinical setting, as well as the ongoing clinical trial ^{18}F-DCFPyL, that salivary gland accumulation of EuK radiotracer is significantly lower in mice compared to humans. There are also interspecies difference in umami (glutamate) taste sensitivity. For example, the mouse umami receptor (mT1R1/mT1R3) is significantly less responsive to glutamate than the human (hT1R1/hT1R3) counterpart (42).

3.6. Investigational Product

^{18}F-DCFPyL is a sterile, non-pyrogenic, radioactive diagnostic agent for intravenous administration, formulated in phosphate buffered sterile water for injection, and containing up to 8% of ethanol.

Name:	2-(3-(1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino] pentyl)ureido)-pentanedioic acid
Abbreviation:	^{18}F-DCFPyL
Form:	Sterile solution
Administration:	Intravenous
Expiration:	6 hours after end of synthesis

MSG is not regulated as a drug product in Canada. It is freely available on the market as a taste enhancer.

3.7. ^{18}F-DCFPyL

^{18}F-DCFPyL is a radiopharmaceutical developed at Hopkins (43), with high accumulation in prostate cancer and favourable distribution for imaging (9). ^{18}F-DCFPyL behaves like ^{68}Ga-PSMA, with higher standardized uptake value (SUV) in tumours (7). The routine production of ^{18}F-DCFPyL has recently been greatly simplified in recent years (44, 45).

4. Rationale for Study

Prostate cancer is the most common cancer affecting Canadian men and many men die from metastatic castration resistant prostate cancer (mCRPC), an incurable form of the disease. Lutetium-177 (^{177}Lu) and Actinium-225 (^{225}Ac) are Radioligands based on the EuK backbone, targeting the PSMA receptor, are highly promising to improve survival and quality of life in patients with mCRPC, but the main side effect is xerostomia, caused by the accumulation of these compounds in the salivary glands. MSG has proven effective, in large doses, to reduce off-target kidney and salivary gland accumulation of EuK based PSMA radioligands, without negatively affecting tumour uptake. We propose to use an imaging radiopharmaceutical, ^{18}F-DCFPyL, to investigate whether MSG can reduce off-target accumulation of PSMA radioligands. ^{18}F-DCFPyL will be used as a surrogate for ^{177}Lu and ^{225}Ac therapeutic radiopharmaceuticals. This way, if MSG is ineffective, affects tumour uptake, or has paradoxical effects by enhancing salivary gland accumulation, this will not adversely affect participants, as ^{18}F delivers minimal radiation exposure and will not have any biological effects even if its biodistribution is altered by MSG.

5. Risks and Benefits

5.1. Radiation exposure

A pilot study of ^{18}F-DCFPyL in humans showed no serious adverse effects with ^{18}F-DCFPyL administration. Minor adverse events were reported but none could be attributed to the radiotracer (9). Participants will receive an effective radiation dose of 0.0165 mSv/MBq, which equates to 5.3 mSv for a typical adult injected dose of 320 MBq (7, 9). The radiation dose from the low-dose CT component of the PET/CT is approximately 3.9 - 7.8 mSv, dependent on body habitus. The typical total absorbed dose to a participant from a ^{18}F-DCFPyL PET/CT is approximately 8.8-16.4 mSv. As the participants will receive two ^{18}F-DCFPyL PET/CT scans as

part of this study, the radiation exposure will be 17.6 to 32.8 mSv. This is considered acceptable for such studies in the adult population. For comparison, a typical diagnostic CT scan of the abdomen and pelvis provides 14 mSv of radiation exposure.

As this is a sub-study of ^{18}F-DCFPyL PET/CT research study, with an additional PET/CT scan and oral administration of MSG or placebo, there is no additional anticipated benefit from participants participating in this study.

5.2. Oral MSG administration

As discussed above, MSG is nontoxic, even in large quantities with a no adverse event limit of 3.2 g/kg based on animal studies. The effects of MSG in humans are debated and have been extensively reviewed. Some studies have reported transient rise in blood pressure, headaches, dizziness and gastrointestinal disturbances such as nausea, when administered in doses in excess of 3 g. A potential link with asthma exacerbations has been suggested, but not substantiated. Large doses of MSG have been safely administered orally or intravenously in human participants, up to 12.7 g in a single oral dose or 125 mg/kg/day over several days.

6. Mode of Administration and Dose

^{18}F-DCFPyL is injected intravenously using an intravenous catheter to avoid extravasation, following the procedures in REB protocol H16-01551 ([^{18}F]-DCFPyL Positron Emission Tomography / Computed Tomography (PET/CT) for Assessment of Recurrent Prostate Cancer").

7. GCP and Regulatory Compliance

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines as set out by Health Canada and the UBC/BC Cancer Research Ethics Board (REB).

8. Target Population

Participants that are eligible to participate in study H16-01551 ([^{18}F]-DCFPyL Positron Emission Tomography / Computed Tomography (PET/CT) for Assessment of Recurrent Prostate Cancer").

9. Trial Objective and Purpose

The objective of this study is to evaluate the effects of oral MSG administration on the biodistribution of ^{18}F-DCFPyL. The eventual purpose is to evaluate whether orally administered MSG is a suitable means of reducing adverse events and normal organ radiation exposure when PSMA-targeting radiopharmaceuticals are used to treat metastatic prostate cancer.

9.1. Hypothesis

Orally administered MSG can significantly reduce lacrimal, salivary gland and renal accumulation of ^{18}F-DCFPyL on PET/CT imaging.

10. Trial Design

10.1. Endpoints

Primary endpoint:

- To evaluate the effects of orally administered MSG on salivary gland accumulation of [^{18}F]-DCFPyL.

Secondary endpoints:

- To evaluate the effects of MSG on renal accumulation of [^{18}F]-DCFPyL.
- To evaluate the effects of MSG on tumour accumulation of [^{18}F]-DCFPyL.
- To evaluate the tolerability and compliance with an orally administered solution of MSG.

Study Design

This is a prospective double blind intra-participant comparison of [^{18}F]-DCFPyL PET/CT scans performed after orally administered MSG or placebo.

The participants will receive oral administration of 12.7 g of MSG or placebo, in two different examination sessions, 30 minutes before [^{18}F]-DCFPyL injection.

10.2. Screening and Enrollment

Participants will be contacted from the list of patients eligible for REB protocol H16-01551 ([^{18}F]-DCFPyL Positron Emission Tomography / Computed Tomography (PET/CT) for Assessment of Recurrent Prostate Cancer"). The patients will be invited to participate in this sub-study, with the clear understanding that declining to participate in this sub study will not affect their eligibility to participate in H16-01151.

10.3. Obtaining Informed Consent

To avoid any impression of coercion, the treating oncologist will not be involved in obtaining consent from participants directly. Following identification of potential research participants by their oncologist, the study coordinator will make contact with the potential participant via phone to discuss the research study and address any questions. Participants are informed that consent is entirely voluntary and that they can withdraw from the study at any time without explanation. They will also be informed that if they decline to participate in this sub-study, this

will not affect their eligibility to participate in H16-01151. They will be informed that participating in this sub-study will entail an additional visit to BC Cancer and an additional scan, and that they will be compensated financially for their time and inconvenience. They will continue to receive the best care at the British Columbia (BC) Cancer regardless of their decision to participate in the study.

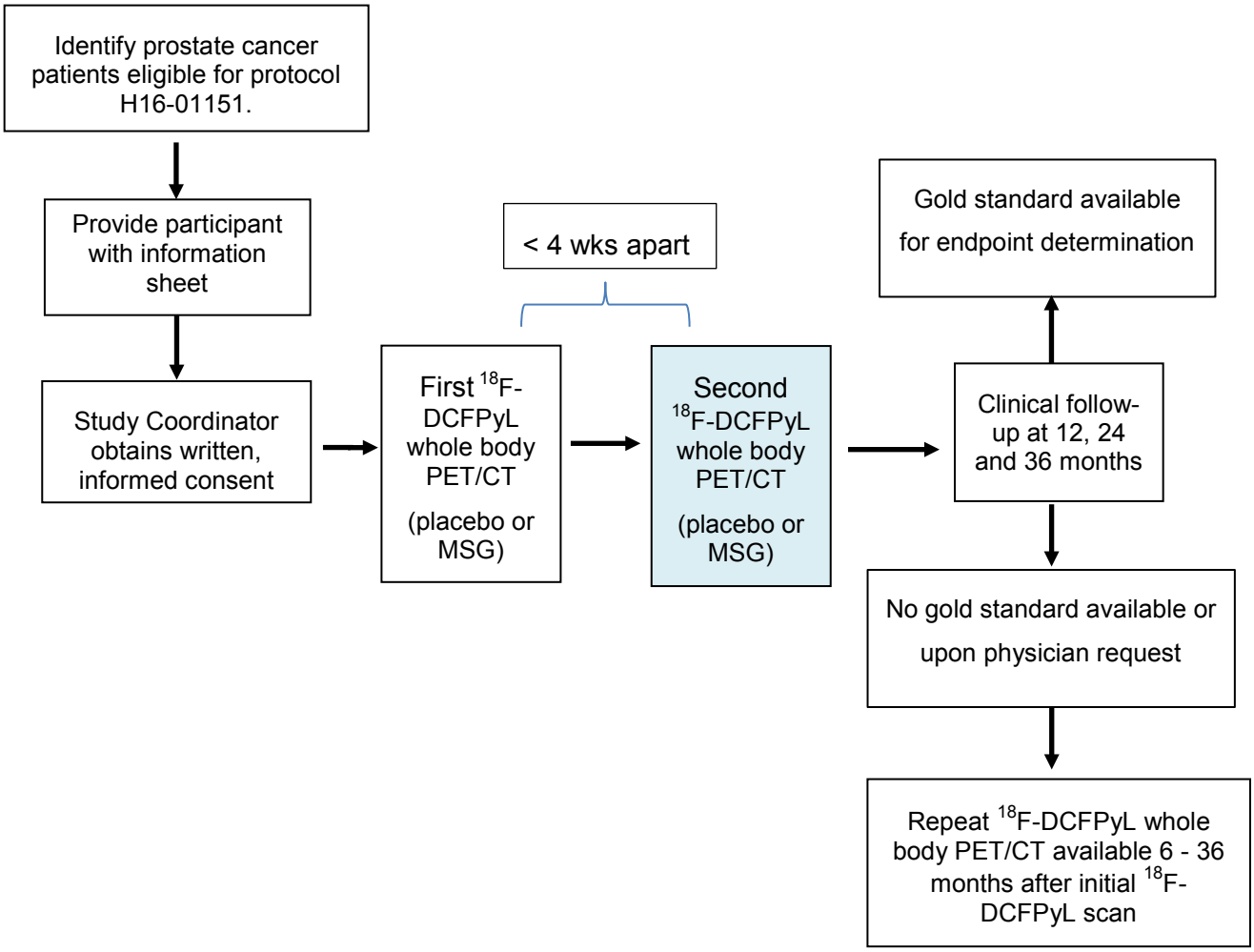
The study coordinator will obtain verbal consent over the phone and will schedule a PET scan appointment. When the participant arrives for their scheduled appointment, a written informed consent will be obtained prior to the performance of any protocol-specified procedures, both for the main study (H16-01551) as well as this sub-study. Participants will be given a copy of the signed consent forms for their own records. A screening log will be maintained to record every participant contacted to participate in the study.

10.4. Assignment of Participant Identification Numbers

The participant identification numbers will be established upon signature of the consent form, and will be consecutively numbered based on the template “MSG-XX-YYY-Z”, where XX represents the site code (01 in this case for BC Cancer), YYY represents the participant number, starting from 001 and numbered consecutively, and Z will be a letter (A or B) to identify whether this is the first or second scan performed as part of this study. The participants will also be assigned an additional study code based on the template required for protocol H16-01151. The placebo examination will be used for the purposes of protocol H16-01151.

10.5. Schematic Flow Diagram

The procedure in blue is the additional PET/CT scan involved in this sub-study. The other components are part of protocol H16-01151.



10.6. Measure to Minimize/Avoid Bias

This is a randomized double blind study, and neither the participant nor the research coordinator collecting adverse events will know whether the participant received placebo or an oral dose of MSG. Clinical information will be extracted on case report forms (CRFs), labelled with the participant identification number. Each imaging data set will contain only the participant identification number, date of exam, and will be fully anonymized. The PET/CT images will be read and analyzed by a small group of board certified nuclear medicine physicians in a core laboratory to minimize interpretation bias. The readers will be blinded as to whether the participants received placebo or MSG.

10.7. Trial Procedures

10.7.1. ^{18}F-DCFPyL PET/CT

Each participant will undergo two ^{18}F-DCFPyL PET/CT scans. Each of the ^{18}F-DCFPyL PET/CT should be performed within 4 weeks of each other. In cases of unexpected delays due to radiotracer unavailability, instrument failure, or participant schedule, additional delays are permissible with authorization from the local site investigator, but every effort should be made to obtain the two scans as closely as possible in time.

The overall procedures will follow that of the parent protocol (H16-01151) for each PET/CT scan, with the following changes:

For the MSG study, food grade MSG (12.7 g) will be dissolved in 300 mL ± 5% low sodium tomato juice (Heinz 50% less salt), and administered orally before ^{18}F-DCFPyL administration.

For placebo administration, regular tomato juice (Heinz) will be used.

Participants will be instructed to drink 300 mL ± 5% of tomato juice containing MSG or placebo starting 30 minutes prior to ^{18}F-DCFPyL injection, preferably over a period of 15-30 minutes, subject to individual tolerance. Participants will be instructed to drink the entire solution. If the participants are unable to completely drink the solution, this will be noted and the residual volume will be measured to calculate the amount of MSG or placebo ingested. As with the ^{18}F-DCFPyL protocol, participants will be instructed to fast for 4 hours prior to the study.

Upon arrival at the PET imaging department, participants will have their weight recorded and baseline vital signs (blood pressure, heart rate, and oxygen saturation level) measured prior to the start of MSG ingestion, immediately prior to ^{18}F-DCFPyL injection and 5 to 15 minutes after injection.

Each study participant will have an intravenous catheter inserted. The participant will receive a bolus intravenous dose of ^{18}F-DCFPyL from an approved supplier, at a dose of approximately 296 MBq followed by a 5 to 20 mL normal saline flush.

The participant will rest in a comfortable chair or bed for 60 minutes. After 60 min, the blood pressure, heart rate, and oxygen saturation levels will be recorded. The participants will be allowed to leave the Functional Imaging Department to get a meal of their choice. The blood pressure, heart rate, and oxygen saturation levels will be recorded again two hours after ^{18}F-DCFPyL. Immediately before scanning, the participants will be taken to a designated washroom and asked to void.

The rest of the procedures will be identical to protocol H16-01151. The PET/CT image acquisition time will be approximately 30 minutes.

Upon completion of the scan, participants will be free to leave the department and will be encouraged to drink 3 to 4 extra glasses of water by the end of the day to promote further clearance of any remaining radiotracer in the urinary tract. Overall, the study will take approximately 3.5 hours of the participant's time for each scan.

10.7.2. Clinical Assessment

The clinical assessment will remain unchanged from the parent protocol. Only the placebo scan (unless the patient withdraws from this sub-study) will be used for data analysis in protocol H16-01151.

10.8. Study Duration and Follow-up Visits

10.8.1. Study Duration

This study will continue until all participants are enrolled, or protocol H16-01151 is discontinued whichever occurs first.

10.8.2. Follow-up Assessments

This will follow the procedures implemented for protocol H16-01151.

24 hour follow-up

As per parent study for protocol H16-01151, all participants will be requested to either return to the functional imaging department approximately 24 hours (acceptable range 16-28 hours) after the injection of ^{18}F-DCFPyL or agree to be contacted by phone. The participants will be asked if they experienced any undesirable effects following the administration of ^{18}F-DCFPyL, or in the intervening 24 hours. The local site attending nuclear medicine physician will then make an assessment as to whether these effects are likely related to ^{18}F-DCFPyL administration.

Other follow-up and subsequent ^{18}F-DCFPyL imaging

This remains unchanged from protocol H16-01151.

Discontinuation Criteria for Individual Participants, Parts of Trial and Entire Trial

Research participants may stop their participation in this sub-study at any time, without prejudice. If the treating oncologist believes that participating in this trial may cause prejudice to a participant, he or she can stop the participation of this research participant. The data from

participants with incomplete participation will be included in the final analysis for efficacy if there is sufficient information to clarify the status of ^{18}F-DCFPyL findings. If the participant initially intends to participate in this sub-study but subsequently chooses to only undergo one of the two scans, the data from the scan that has been obtained (whether in the placebo or MSG group) will be reported clinically and used for data analysis in protocol H16-01151. Participants who withdraw from the study will be replaced by other participants for the purpose of this sub-study so that a total of 10 participants with two scans (MSG and placebo) are enrolled.

Given that there is already a good safety profile with ^{18}F-DCFPyL as well as MSG, no serious adverse events are expected in this study. If, however, a serious adverse event is reported and attributed to the injection of ^{18}F-DCFPyL, then as per protocol H16-01151, the ^{18}F-DCFPyL scans will stop immediately until an investigation of the adverse event has been performed, as well as a review of the manufacturing, quality control data and procedures from the ^{18}F-DCFPyL production site. If a serious adverse event is reported and attributed to the ingestion of MSG, then this study will stop immediately until an investigation of the adverse event has been performed. If it is not clear whether the ^{18}F-DCFPyL or the MSG causes the serious adverse event, both studies will stop until an investigation of the adverse event has been performed. All serious adverse events must be reported as described below.

If funding for the study is discontinued or lapses due to unexpectedly slow accrual and attempts to obtain further funding fail, then the study may be interrupted and the results of participants accrued to date will be compiled and analyzed.

11. Accountability Procedures for the Investigational Product

The ^{18}F-DCFPyL product will be manufactured at the approved radiopharmaceutical manufacturing site under a Health Canada approved Clinical Trial Application (CTA). The manufacturer of the product is responsible to meet Health Canada requirements for sterility. All serious adverse events must be reported to the manufacturer of ^{18}F-DCFPyL, and the local REB as described below.

12. Trial Treatment Randomization Codes and Procedures for Breaking Codes

All data will be anonymized. Nominal data will be replaced with the research participant code. The study site coordinator will keep a master list of participant identification data associated with the research participant code. This master list will be kept separate from the CRFs, and will be kept under lock and key.

For randomization, a computer generated random list will determine the order of the scans (MSG first, placebo first). Sealed envelopes will be prepared. A study coordinator or technologist not involved in measuring vital signs or collecting adverse events will prepare the tomato juice solution based on the randomization envelope. The rest of the team will not be informed of which tomato juice is used (placebo or MSG) but this information will be recorded and will be immediately accessible should a participant experience a severe adverse event.

13. Data

Nominal participant data will only be kept in the master list kept by the local site coordinator. The data collected in the CRF for participant demographic data will be the same as per protocol H16-01151.

14. Selection and Withdrawal of Participants

14.1. Record of Study Participants

A confidential record will be maintained of all study participants, including all participants who were screened for the study but not actually studied under this protocol. This confidential record will include at least the participant's name, hospital records number, and address in the event of an emergency, if any further follow-up is necessary.

14.2. Participant Inclusion Criteria

The same inclusion criteria for the primary study protocol H16-01151 will apply.

14.3. Participant Exclusion Criteria

The same inclusion criteria for the primary study protocol H16-01151 will apply, with the addition of the following:

- Severe uncontrolled hypertension (systolic blood pressure above 140 mm Hg and diastolic blood pressure above 90 mm Hg, or systolic blood pressure above 180 mm Hg, or diastolic blood pressure above 110 mg Hg). Patients with controlled hypertension under medication are eligible.
- History of severe asthma that has led to hospitalizations or emergency room visits.
- History of intolerance to MSG.
- History of severe headaches or migraines triggered by food or MSG.
- Participants on a sodium/salt restricted diet due to other medical conditions.
- No new treatment has started between the first and second ^{18}F-DCFPyL PET/CT.

14.4. Participant Withdrawal

Participants are free to withdraw from the study at any time. If a participant decides to withdraw during the PET/CT scan, they are brought out of the scanner immediately. Just as if they had completed the scan, an appreciation for their time and effort invested in participating in this research will be expressed to the participant. If an injection of ^{18}F-DCFPyL took place, the participant is reminded to drink 3 to 4 extra glasses of water by the end of the day to accelerate elimination of residual radioactivity from the urinary system. Data collected from the withdrawn participant will be used if there is sufficient information to evaluate the relative accuracy of the PET scan. Participant withdrawal from the research study will not jeopardize the participant's care.

15. Treatment of Participants

Not applicable. The participants will be treated by their care team according to routine procedures. Treatments are not affected by participation in this clinical trial, and participants recruited in this trial can participate in other research projects, as long as these projects do not interfere with the scheduling of the imaging studies.

16. Study Materials

Name:	^{18}F-DCFPyL
Activity:	296 - 521 MBq per participant
Dosage Form:	Sterile solution

Product is prepared on a scheduled basis; the lot number of each product administered to each participant will be recorded on the dose slip or sticker. The expiry date (6 hours after end of synthesis) is noted on the label.

The study agent will be synthesized in-house in the radiopharmaceutical facility once all essential regulatory documents are available, including written approval from Health Canada and appropriate REB approval.

The MSG used in this study will be the Ajinomoto Monosodium Glutamate Umami Seasoning in 454g bags, obtained from a distributor. MSG is an unregulated taste enhancer in Canada and is available from grocery stores and food distributors. To ensure the safety and integrity of the product, bags of MSG will be kept under lock and key in a secure temperature and humidity controlled storage room used for manufacturing precursors for human clinical studies in the cyclotron radiopharmacy.

16.1. Authorized Suppliers

BC Cancer - Vancouver, will be the authorized radiopharmaceutical facility authorized to manufacture ^{18}F-DCFPyL, pending approval by Health Canada as part of a CTA.

Ajinomoto Monosodium Glutamate Umami Seasoning in 454g bags, will be sourced via Amazon Canada.

16.2. Preparation

The study agent (^{18}F-DCFPyL) is prepared in a shielded multi-dose vial. Using appropriate shielding and aseptic technique, the proper amount of ^{18}F-DCFPyL will be drawn up into a sterile syringe. The final total dose will be measured in a dose calibrator and entered on the ^{18}F-DCFPyL dose slip/sticker.

The MSG solution will be prepared by weighing 12.7 g of MSG in an empty disposable plastic glass, to which 300 mL ± 5% of Heinz low sodium tomato juice will be added.

The placebo solution will be constituted of regular Heinz tomato juice.

16.3. Packaging and Labelling

^{18}F-DCFPyL is supplied in a multi-dose, sterile, non-pyrogenic injection vial. The vial is labelled with an immediate surface label containing the name, lot number and date of preparation and an outer label containing the following:

- Name and concentration (assay) of ^{18}F-DCFPyL
- Lot number
- Calibration date and time
- Total activity and total volume
- Radiation warning symbol and “DANGER - RADIATION”
- Store upright at room temperature (15-30°C)
- Expiration period (6 hours after end of synthesis)
- Manufacturer’s name and address

A sample of each bag of MSG used in this study will be retained in case serious adverse events are reported by participants.

16.4. Storage and Disposition of Study Agent

The multi-dose vial containing the ^{18}F-DCFPyL will be stored at room temperature in a shielded area. All regulations regarding the handling of radioactive material will be followed.

The investigator or designee is responsible for ensuring that the ^{18}F-DCFPyL is correctly dispensed and recorded, that the product is handled and stored safely and properly, and that it only be given to participants in accordance with this protocol. Records of dispensing of ^{18}F-DCFPyL will be kept on a Study Medication Inventory Form.

Unused and used ^{18}F-DCFPyL containers must be reconciled and disposed of according to the trial site's procedures for handling radioactive material.

17. Assessment of Efficacy

17.1. Efficacy Parameters

Salivary gland and renal accumulation of [18F]-DCFPyL measured by the SUV.

17.2. Methods for Assessing and Analyzing Efficacy

^{18}F-DCFPyL scans will be analysed as per protocol H16-01151.

For determination of salivary gland and renal uptake, regions of interest will be drawn around the kidneys and salivary glands, using a standardized contouring method, to measure the SUV. The average SUV in the organs will be used for this analysis. Additional regions of interest will be placed on the 5 most active lesions on the scan, the circulating blood activity (from the left ventricle cavity), the liver, and skeletal muscles as background activity.

18. Assessment of Safety

18.1. Methods for Analyzing and Assessing Safety

^{18}F-DCFPyL quality will be determined so as to meet the approved specifications for production.

All participants will be weighed prior to ^{18}F-DCFPyL injection. Before administration of MSG, before injection of ^{18}F-DCFPyL, 5 to 15 minutes after ^{18}F-DCFPyL injection and one and two hours after ^{18}F-DCFPyL injection, vital signs (blood pressure, heart rate, oxygen saturation) will be recorded. If there are concerns that the participant's health status has changed prior to, during, or immediately following the PET/CT scan, a physician will provide a more detailed assessment. There are no anticipated side effects from the ^{18}F-DCFPyL injection itself.

18.2. Adverse Event Reporting

The framework used for adverse reaction recording will be based on the American College of Radiology Imaging Network (ACRIN) guidelines published September, 2002 (revised May, 2008).

18.3. Site Responsibilities

Each study investigator, study nurse and/or coordinator is responsible for the prompt reporting of adverse events. The assignment of the event grade and association with the investigational drug is made by the study site investigator, and should be documented in the participant chart. An adverse event form must be completed within 30 days. Serious adverse events should be reported to the local REB within 48 hours following the event, and unexpected SAEs attributed to the study drug must be reported to Health Canada by fax at (613) 957-0364 within 7 days for a fatal or life-threatening event or 15 days for a non-fatal or non-life-threatening event.

18.4. Definition of Adverse Event

An Adverse Event (AE) is any untoward, undesired, unplanned medical occurrence in a participant and does not necessarily have a causal relationship with the study intervention. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding or physiological observations), symptom or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. Any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study, including inter-current illnesses or injuries, should be regarded as an adverse event.

18.5. Definition of Serious Adverse Event

Adverse events are classified as serious or non-serious. A Serious Adverse Event (SAE) is defined as any untoward medical occurrence/AE that:

- Results in death;
- Is life-threatening (refers to any adverse event that places the participant at immediate risk of death from the event as it occurred; life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death);
- Requires in-patient hospitalization and/or prolongation of an existing hospitalization (hospitalization refers to an overnight admission). Emergency room visits are not

considered serious until one of the above criteria is met. Any elective hospitalization for a pre-existing condition that has not worsened does not constitute an SAE;

- Results in persistent or significant disability or incapacity (substantial disruption in a person's ability to conduct normal daily living activities); a congenital anomaly or birth defect; or other medically important event.

Important medical events are those based upon appropriate medical judgment that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the participant and may require intervention to prevent one of the other serious outcomes noted above. If there is any doubt whether the adverse event constitute a serious adverse event, it should be treated as serious and reported.

Grade refers to the severity (intensity) of the adverse event.

1 - **Mild**: AE is noticeable to the participant but does not interfere with routine activity.

2 - **Moderate**: AE interferes with routine activity but responds to symptomatic therapy/rest

3 - **Severe**: AE significantly limits the participant's ability to perform routine activities despite symptomatic therapy

4 - **Life-threatening or disabling**

5 - **Death/Fatal**

18.6. Adverse Event Attribution

Attribution is the determination of whether an adverse event is related to a study treatment or procedure. An AE may be considered associated with the study treatment or procedure if there is a reasonable possibility that the adverse event was caused by the injected ^{18}F-DCFPyL. An AE may be considered not associated with the study treatment/procedure if there is not a reasonable possibility that the AE was caused by participating in the study.

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.

18.7. Expected Adverse Events from procedures

Injection of ^{18}F-DCFPyL

- Bruising
- Bleeding, or
- Infection at the site of injection

PET/CT scan

- Discomfort, or
- Claustrophobia

MSG

Anectodal evidence has linked MSG to the following symptoms, with no clear scientific evidence of causality:

- Headache
- Flushing
- Sweating
- Facial pressure or tightness
- Numbness, tingling or burning in the face, neck and other areas
- Heart palpitations
- Chest pain
- Nausea
- Weakness

Only AEs that are attributed to the study drug and are both serious and unexpected will be participant to expedited reporting to Health Canada and to the local REB. Each centre must adhere with the policy of documenting any AE, regardless of causality.

18.8. Adverse Event Follow-up after ^{18}F-DCFPyL

The AE monitoring period in the protocol follows the American College of Radiology Imaging Network (ACRIN) recommendations of monitoring events until 10 half-lives of the agents. The study is conducted in participants with cancer who are likely to suffer from significant events related to their disease or toxicity caused by treatments unrelated to this research study. For this reason, ACRIN does not recommend extending the monitoring period further due to the risk of confounding investigational product AEs with treatment-related AEs. AEs will be considered

related to this study if they occur within 10 half-lives (rounded up to the next day) following the administration of ^{18}F-DCFPyL. Consequently, this would mean reporting AE occurring up to 24 hours following administration.

18.9. Type and Duration of Follow-up of Participants after Adverse Events

An AE should be followed by the study site lead investigator until the event is resolved, the participant is lost to follow-up, the symptoms resolve, or the AE is found to be unrelated to the study.

19. Statistics

19.1. Description of statistical methods

19.1.1. Statistical analyses

The ^{18}F-DCFPyL results will be analysed as comparison between the MSG and placebo subgroup. Standard descriptive statistics will be used for the SUV values, including mean, median, and standard deviation.

SUV values will be assessed for normality and transformed using standard techniques such as square root or reciprocal transformation when appropriate. If the data pass a normality test (D'Agostino normality test or other to be determined), organ uptake in the kidneys and salivary glands will be performed using a one-tailed paired t-test, with a p-value of 0.05 (the a priori hypothesis is a reduction in renal and salivary gland accumulation in the MSG group).

If the data does not readily conform to a normal distribution, parametric analyses will be used, notably the Wilcoxon matched-pairs signed-rank test for the a priori hypotheses, and Dunn's test for the other organs.

As a supplemental analysis, since the SUV is a ratio that is normalized based on either lean body mass and the injected activity of the radiopharmaceutical, analysis of covariance will be performed with the organ uptake (kidney and salivary glands) as the dependent variable, with the treatment group as the independent variable, and body mass and injected activity as covariates. This will be performed looking as well at the lean body mass and body surface area as covariates instead of body weight.

Safety parameters will be presented using descriptive statistics.

19.2. Sample Size Considerations

A total of 10 participants in a paired experiment will be used for this study. In a preliminary analysis of 100 ^{18}F-DCFPyL scans performed to date, the SUV (based on body weight) in the parotid glands was 15.2 ± 4.7, while the SUV in the kidneys was 34.2 ± 12.7. Clinically, a reduction of 33% of more would be considered sufficiently significant to consider using an intervention such as MSG to reduce radiation dose to the salivary glands and kidneys.

19.2.1. Primary endpoint

The aim of this pilot study is to evaluate if a reduction in salivary gland accumulation of ^{18}F-DCFPyL can be achieved with MSG. A sample size of 10 achieves 100% power to detect a mean of paired differences of 5.0 (33%) with an estimated standard deviation of differences of 1.0 and with a significance level (alpha) of 0.05 using a one-sided paired t-test. If the estimated standard deviation of differences is 5.0, a sample size of 10 achieves 90% power to detect a mean difference of 5.0 with an alpha of 0.05. These calculations were performed using NCSS Pass software, version 14.0.6, using the Paired Means Power Analysis tool.

19.2.2. Secondary endpoints

For the secondary analysis of renal accumulation, a sample size of 10 achieves 100% power to detect a mean of paired differences of 11.4 (33%) with an estimated standard deviation of differences of 2.0 and with a significance level (alpha) of 0.05 using a one-sided paired t-test. If the estimated standard deviation of differences is 10.0, a sample size of 10 achieves 95% power to detect a mean difference of 11.4 with an alpha of 0.05.

Tumour uptake is highly variable among sites (due to size variations) and across participants, but expected to be reproducible to within 10% within participants and within target lesions, based on prior experience with ^{18}F-FDG PET imaging on test-repeat experiments. A reduction of 10% or greater would be highly undesirable for the intervention. Assuming a mean difference of 1.1 or greater, and standard deviation of the difference ranging from 0.1 to 1.0, the table below shows the power of the study:

Paired Means Power Analysis

Numeric Results for Paired T-Test
Null Hypothesis: Mean of Paired Differences = 0, Alternative Hypothesis: Mean of Paired Differences > 0
Unknown standard deviation.

Power	N	Alpha	Beta	Mean of Paired Differences	S	Effect Size
1.00000	10	0.05000	0.00000	1.1	0.1	11.000
1.00000	10	0.05000	0.00000	1.1	0.5	2.200
0.94020	10	0.05000	0.05980	1.1	1.0	1.100

For adverse events, simple descriptive statistics will be used. Differences in vital signs between the MSG and placebo groups will be performed using repeated measures analysis of variance.

19.3. Criteria for the Termination of the Trial

The trial will be terminated when participant accrual is complete for the primary objective, if severe adverse events are observed in the MSG group and the REB recommends interruption of the study, or if the primary protocol is terminated.

19.4. Accounting for Missing, Unused and Spurious Data

A minimum of two scans per participant will be required for this study for analysis (placebo vs MSG). Participants who have not completed two scans will be replaced by other participants.

19.5. Procedures for Reporting Protocol Deviations

Any deviation from the protocol must be reviewed and approved by the investigators listed on the title page of this protocol, and a request for acknowledgement must be submitted to the institution's Research Ethics Board.

19.6. Selection of Participants to be Included in the Analyses

All evaluable participants will be included in the analyses.

20. Direct Access to Source Data/ Documents

The data gathered from the scans must be stored on a password protected computer system and hosted on a secure network at the study site.

Participant study information including reconstructed PET/CT data stored on compact disc, consent forms and case report forms are filed and stored in a locked room at the study site. The identification numbers correlating with participant personal/medical information are kept as per medical records in a locked cabinet in a locked office. Only study centre personnel may

have access to these records. The local site REB, study sponsor and representatives from Health Canada may also review the records and this is indicated in the participant consent form.

21. Data Management

All procedures in the original approved parent protocol (H16-01551) apply to this study.

22. Ethical Considerations

All procedures in the original approved parent protocol (H16-01551) apply to this study**.**

23. Regulatory Requirements and Investigator Obligations

23.1. GCP and Investigator Compliance

This study will be conducted in accordance with the principles of GCP guidelines as issued by the ICH (1996) and adopted by Canada in 1997. To ensure compliance with the guidelines, the study may be independently audited. The investigator agrees, by written consent to this protocol, to fully co-operate with compliance checks by allowing direct access to all documentation for authorized individuals.

23.2. Documentation and Record-Keeping

The investigator must maintain all study records, including participant medical records, for 25 years after the completion or termination of this clinical trial.

23.3. Premature Termination of the Study

If the clinical study must be terminated for any reason whatsoever, the investigator will return all study agents and CRFs to the Sponsor, provide a written statement as to why the premature termination has taken place and notify the REB and Health Canada.

23.4. Clinical Study Report / Publication

All procedures in the original approved parent protocol (H16-01551) apply to this study**.**

23.5. Compensation / Indemnification

No funding is available to compensate participants for any injury related to procedures performed as part of this clinical trial.

The investigator will retain any indemnification and insurance documents in the study file and these documents must be available for inspection by the REB and the regulatory authorities.

REIMBURSEMENT

A reimbursement of up to $100 will be provided for out of pocket expenses such as transportation, parking, meals, etc. if receipts are kept and provided for reimbursement, for each scan.

PAYMENTS TO PARTICIPANTS

Since participants volunteer to undergo a second PET/CT scan as part of this study with no expected benefits, and the inconvenience of an IV injection, time spent in the facility, and potential minor undesirable effects of MSG, a compensation will be offered. Research participants will receive payment for the extra scan that they will undergo as part of this research study, prorated to the extent of their participation. In no case will payment be conditional on completion of the entire study. If participants withdraw early, they will be compensated in proportion to their participation as per below.

Payment is calculated on the following basis and based on an average hourly salary rate in Canada in 2016 of $27.70 per hour.

3.5 hours of participant time x $27.70 = $100
Injection: $50
Radiation exposure: $100
Total maximum: $250.00 per participant

23.6. Protocol Amendments

Changes to a protocol must be implemented by a formal protocol amendment. A formal amendment, drafted, and approved by the Principal Investigator, must be approved by the REB prior to implementation of the amendment.

In the case where the original clinical trial was submitted to Health Canada as a CTA, and the protocol amendment will affect (1) the selection, criteria for selection, monitoring or dismissal of a clinical trial participant; (2) the evaluation of the clinical efficacy of the drug, (3) alter the risk to the health of a clinical trial participant; (4) the safety evaluation of the drug or (5) extend the duration of the clinical trial, Health Canada must approve these changes, by means of a CTA amendment, before they are implemented. If the protocol amendment does not affect any of the 5 aspects of a clinical trial outlined above, the changes may be implemented immediately, but

Health Canada must be informed in writing, by means of a Notification, within 15 calendar days after the date of implementation of the amendment.

In some instances, an amendment may require a change to a consent form. The investigator must receive REB approval of the revised consent form prior to implementation of the amendment. In addition, changes to the CRFs, if required, will be incorporated in the amendment.

A modification to the protocol may be initiated without REB or Health Canada approval ONLY when the change is necessary to eliminate an apparent immediate hazard to the participants and on approval by the Principal Investigator. In that event, the investigator must notify the REB in writing within five (5) working days after implementation and the Principal Investigator must supply Health Canada with a CTA amendment or Notification, as appropriate, within 15 days after implementation.

24. Financing and Insurance

All procedures in the original approved parent protocol (H16-01551) apply to this study.

25. Supplements

The following documents contain important information on this protocol:

- Main consent form for - ^{18}F-DCFPyL Positron Emission Tomography / Computed Tomography (PET/CT) for Assessment of Recurrent Prostate Cancer
- Protocol H16-01551 ([18F]-DCFPyL Positron Emission Tomography / Computed Tomography (PET/CT) for Assessment of Recurrent Prostate Cancer")
- Sub-study consent form - Participant Information and Consent Form – Evaluation of monosodium glutamate (MSG) to reduce salivary gland and renal accumulation of PSMA-binding radiopharmaceuticals
- Investigator's brochure for ^{18}F-DCFPyL injection

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