EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 May 2023
EMA/CHMP/279917/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pylclari

International non-proprietary name: piflufolastat (18F)

Procedure No. EMEA/H/C/005520/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Pylclari
Applicant:	Curium Pet France Biopole Clermont Limagne 3 Rue Marie Curie 63360 St Beauzire FRANCE
Active substance:	piflufolastat (18F)
International Non-proprietary Name/Common Name:	piflufolastat (18F)
Pharmaco-therapeutic group (ATC Code):	V09IX16
Therapeutic indication(s):	This medicinal product is for diagnostic use only. Pylclari is indicated for the detection of prostate-specific membrane antigen (PSMA) positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings: • Primary staging of patients with high-risk PCa prior to initial curative therapy, • To localize recurrence of PCa in patients with a suspected recurrence based on increasing serum prostate-specific antigen (PSA) levels after primary treatment with curative intent. Pylclari is indicated for use with positron emission tomography (PET).
Pharmaceutical form(s):	Solution for injection
Strength(s):	1000 MBq/ml 1500 MBq/ml

Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

Table of contents

List of abbreviations

ADT	Androgen deprivation therapy
AE	Adverse event(s)
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
ASR	Age-standardised rates
AUC	Area under the curve
BCR	Biochemical recurrence
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CIM	Conventional imaging modalities
CLR	Correct localisation rate
CT	Computed Tomography
CTCAE	Common terminology criteria for adverse events
18F-DCFPyl	2-(3-(1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido) pentanedioic acid, piflufolastat (18F)
DR	Detection Rate
EANM	European Association of Nuclear Medicine
EAU	European Association of Urology
EBRT	External Beam Radiation Therapy
EC	European Commission
ECG	Electrocardiogram
ECOG-PS	Eastern Cooperative Oncology Group-Performance Status
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
eLND	Extended lymph node dissection
ePLN	Extra pelvic lymph node
EMA	European Medicines Agency
EU	European Union
18F-FCH	Fluorocholine (18F)
FDA	Food and Drug Administration
FDG	Fludeoxyglucose (18F)

FT-IR	Fourrier Transform Infrared Spectroscopy
FN	False negative
FP	False positive
FPFV	First patient-first visit
GC	Gas Chromatography
GCP	Good Clinical Practices
GCPII	Glutamate carboxypeptidase II
GG	Grade group
GS	Gleason score
HLB	Hidrophilic-lipophilic balance
HPLC	High performance liquid chromatography
ISS	Integrated Summary of Safety
ISUP	International Society of Urological Pathology
i.v.	Intravenous(ly)
IQR	Interquartile range
KF	Karl Fischer titration
LC-MS	Liquid chromatography mass spectrometry
LNCaP	Lymph Node Carcinoma of the Prostate
LPFV	Last patient-first visit
M	Metastasis (staging)
mCRPC	Metastatic castration resistant PCa
MedDRA	Medical Dictionary for Regulatory Activities
MLEs	Maximum likelihood estimates
MMQ	Medical management questionnaires
mpMRI	Multiparametric MRI
MO	Major Objection
MRI	Magnetic resonance imaging
n	Number(s)
N	Node (staging)
NA	Not applicable
NaF	Sodium fluoride
NCI	National Cancer Institute
NCCN	Natinal Comprensive Cancer Network

NMR	Nuclear Magnetic Resonance
NOD	Non-obese diabetic
NPCaT	Non-Prostate Cancer Tumour
NPV	Negative Predictive Value
p	Probability
PCa	Prostate cancer
csPCa	Clinically significant PCa
PET	Positron Emission Tomography
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PLN	Pelvic lymph node
PLND	Pelvic lymph node dissection
pH	Negative logarithm of hydrogen ion concentration
PPV	Positive Predictive Value
PSA	Prostate Specific Antigen
PSAdt	Prostate Specific Antigen doubling time
PSMA	Prostate Specific Membrane Antigen
PT	Preferred Term
PTFE	Polytetrafluoroethylene
QT	QT interval on ECG
RARP	Robotic assisted radical prostatectomy
RBCs	Red blood cells
RCC	Renal Cell Carcinoma
ROIs	Regions of interest
RP	Radical prostatectomy
RT	Radiation therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SCID	Severe combined immunodeficiency disease
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	Standard deviation
SOC	System Organ Class

SOR	Standard of reference
SOT	Standard of truth
SRT	Salvage radiation therapy
SUV	Standardised Uptake Value
TEAE	Treatment-emergent adverse event
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TN	True negative
TNM	Tumour, nodes and metastases
TP	True positive
TZ	Transition Zone
US	United States
vs	Versus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Curium Pet France submitted on 24 June 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for 18F DCFPyL CURIUM, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 December 2019.

The applicant applied for the following indication:

This medicinal product is for diagnostic use only.

18F-DCFPyL CURIUM is used for imaging in patients undergoing oncologic diagnostic procedures describing function or diseases when increased expression of prostate specific membrane antigen is a diagnostic target.

• Initial staging of prostate cancer in patients at risk of metastases, who are candidates for definitive therapy
• Localisation of recurrence in case of rising serum PSA levels after treatment.

(18F) DCFPyL CURIUM is indicated for use with positron emission tomography (PET).

Of note, towards the end of the procedure, the applicant submitted Pylclari as invented name instead of 18F DCFPyL CURIUM.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0357/2019 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance piflufolastat (18F) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 July 2019	EMEA/H/SA/4162/1/2019/III	Dr Armin Koch, Dr Juha Kolehmainen
12 December 2019	EMEA/H/SA/4162/1/FU/1/2019/II	Dr Armin Koch, Dr Markku Pasanen

The Scientific Advice pertained to the following quality, non-clinical and clinical aspects:

- The finished product specifications;
- The non-clinical data package to support a marketing authorization application;
- The proposed clinical development program for an indication in the staging of high-risk prostate cancer patients and localisation of locoregional recurrence, or metastatic disease, including data on diagnostic thinking and therapeutic impact, data from a phase 3 US study; the imaging assessment method; the totality of evidence needed to establish the diagnostic efficacy; the use of the OSPREY study to support the demonstration of the benefit / risk; the calculation of PPV and sensitivity to characterise diagnostic performance in a highly selected patient population in the CONDOR trial; the choice of comparator; the waving of studies to assess the effect on QT or to evaluate special populations.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Maria Concepcion Prieto Yerro Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	24 June 2022
The procedure started on	14 July 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 October 2022

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	14 October 2022
The CHMP Co-Rapporteur's Critique Assessment Report was circulated to all CHMP and PRAC members on	17 October 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	10 November 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 January 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	07 March 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	30 March 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 May 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Pylclari on	25 May 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	25 May 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially applied indication for Pylclari was for the use for imaging in patients undergoing oncologic diagnostic procedures describing function or diseases when increased expression of prostate specific membrane antigen is a diagnostic target; in the following settings:
• Initial staging of prostate cancer in patients at risk of metastases, who are candidates for definitive therapy;
• Localisation of recurrence in case of rising serum PSA levels after treatment.

The finally approved indication for Pylclari is for the the detection of prostate-specific membrane antigen (PSMA) positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings:
• Primary staging of patients with high-risk PCa prior to initial curative therapy;
• To localize recurrence of PCa in patients with a suspected recurrence based on increasing serum prostate-specific antigen (PSA) levels after primary treatment with curative intent.

2.1.2. Epidemiology

Prostate cancer (PCa) is a disease affecting more than 2.3 million men in the United States (US) and around 4 million in Europe. Annually, nearly 181,000 new cases of PCa are diagnosed in the US, coupled with approximately 417,000 newly diagnosed cases in Europe (Ferlay et al., 2013; Siegel et al., 2020).

It is estimated that PCa will affect one in six men in their lifetimes, leading to approximately 261,000 deaths per year in developed countries worldwide (Ferlay et al., 2010).

The mortality from the disease is second only to lung cancer in men. (Ferlay et al., 2013; Siegel et al., 2020). The vast majority of men dying of PCa succumb to metastatic disease.

2.1.3. Biologic features, aetiology and pathogenesis

Prostate-specific antigen is a serine protease enzyme produced by the columnar epithelium of prostatic tissue. The proenzymatic intracellular form of PSA is pro-PSA. Following cellular production, pro-PSA passes through the basal and endothelial cell layers before entering the prostatic ducts, where it is converted to active PSA, finally penetrating the capillary membranes to enter the systemic circulation (Schedlich et al., 1987). A small portion of this active PSA then undergoes proteolysis, becoming inactive or "free" PSA when it enters the bloodstream and remains unbound. Active PSA that reaches the bloodstream rapidly becomes bound to circulating protease inhibitors (Mikolajczyk et al., 2002). The age-adjusted percent free to protein-bound PSA ratio is a useful indicator of cancer as the free PSA/total PSA ratio tends to decrease in malignancy. PSA levels also increase with age. Prostate cancer cells do not produce more PSA than benign cells; in fact, they tend to manufacture less. However, malignant cells will more easily allow PSA to pass through the cell wall into the surrounding extracellular fluid and eventually reach the bloodstream. This is because malignant prostate cells lack a basal layer that would otherwise restrict the passage of PSA outside the cell. Very

high Gleason score cancer cells that are highly undifferentiated may not produce a significant amount of PSA (David and Leslie; 2023).

Prostate-specific membrane antigen is a type II transmembrane glycoprotein, also known as folate hydrolase I or glutamate carboxypeptidase II, and is a biological target for diagnostic imaging and therapy in PCa (Silver et al 1997, O'Keefe et al 2018). PSMA is expressed in normal human prostate epithelium at low levels but may be overexpressed by malignant tissues, particularly by prostate cancer cells, including metastatic disease. PSMA is highly expressed in nearly all prostate cancers, including adenocarcinoma, but has restricted and several hundred-fold lower expression in some normal tissues such as the duodenal mucosa, renal proximal tubules, and salivary glands (Bostwick et al 1998, Sokoloff et al 2000, Chang 2004, Ghosh and Heston 2004). Most of the cancers in the prostate originate in the peripheral zone. The vast majority of prostate cancers are arising from adenocarcinomas. Prostate cancer is generally multifocal and present throughout the gland. The spread of the disease may occur initially through the capsule where the ejaculatory ducts enter the prostate or in the region of the bladder neck and can progress to the seminal vesicles or the bladder to invade the surrounding tissues and muscles. The degree of differentiation has prognostic value and is graded using the Gleason grading system. The scale measures the patterns of growth from 1-5 and the differentiation of cells from well to poorly differentiated. (Humphrey., 2004).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The risk of clinically significant prostate cancer is related to age, ethnicity, family history, PSA level, free/total PSA ratio and findings on digital rectal examination (Thompson et al., 2006). Physicians are encouraged to use risk calculators incorporating these factors.

The clinical picture of PCa is variable and may range between asymptomatic, microscopic, well-differentiated tumour that may never become clinically significant to the rarer screen detected, or clinically symptomatic aggressive, high-grade cancer that causes metastases, morbidity, and death. Diagnostic work-up of PCa is complex. Diagnostic tools include PSA testing, digital rectal palpation, transrectal ultrasound (TRUS), prostate biopsy, and histopathologic examination (Schwarzenböck et al., 2012, Smith et al., 2016, Prasad et al., 2016). Additionally, further imaging techniques such as, magnetic resonance imaging (MRI), bone scintigraphy, computer tomography (CT), and positron emission tomography (PET)/CT with (18F)Fluorodeoxyglucose, (18F)Choline, (11C)Choline and the more recently approved (18F)fluciclovine are used (Schwarzenböck et al., 2012; Nanni et al., 2016, Odewole et al 2016). Two main pivotal time-points in terms of decision-making on treatment strategy are primary staging of PCa, that takes place in the patients with confirmed PCa, before the first definitive therapy is started, and confirmation of PCa recurrence and staging in the patients who developed increased PSA after curative treatment of PCa (i.e., patients with so called biochemical recurrence – BCR). In both cases, gained information can direct clinical decision-making and may have impact on subsequent treatment strategy and clinical outcomes, such as patients' survival.

Detection of small lymph node metastases is a particular challenge for morphological imaging methods because diagnosis of disease typically requires a minimum lesion size (e.g., 10 mm) which precludes the detection of smaller metastases and microscopic disease. In addition, morphological changes are in many cases not specific for PCa but can also occur as the consequence of other conditions such as infection or inflammation, which makes the correct detection of PCa lesions even more difficult (Blomqvist et al., 2014; Hricak et al., 1987; Scheidler et al., 1999; Shinohara et al., 1989).

Hybrid functional and structural imaging modalities such as positron emission tomography (PET) have been increasingly used in the diagnosis and follow-up of PCa. Choline PET-CT radiopharmaceuticals,

which visualize the choline metabolism associated with the tumour cells, are being used in the EU for detection of recurrences of prostate cancer in any location (both local, regional and distant).

Other diagnostic method extensively used is functional imaging used in nuclear medicine, specifically, radionuclide bone scintigraphy, and four metabolic radiopharmaceuticals for direct visualisation of lesions of primary and/or recurrent PCa that are approved for routine use in EU:

- 18F-FCH from several marketing authorisation holders is currently approved for functional imaging of PCa lesions in several EU countries for: *-Initial staging of prostate cancer in high risk patients*; *-Localisation of locoregional or distant recurrence in case of rising serum PSA levels after treatment.*
- 18F-fluciclovine, for: *Detection of recurrence of PCa in adult men with a suspected recurrence based on elevated blood PSA levels after primary curative treatment.*
- gozetotide (PSMA-11) under the trade name Locametz (EMEA/H/C/005488) as a kit for radiopharmaceutical preparation to be radiolabelled with Gallium-68 for:- *Primary staging of patients with high-risk PCa prior to primary curative therapy, - Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy, - Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated*.
- Additionally, the radiopharmaceutical ready for use, 18F-PSMA-1007, under the trade name of Radelumin has been approved in some Member States with two strengths, 1300 MBq/mL and 2000 MBq/mL, for:- *Primary staging of patients with high-risk PCa prior to primary curative therapy; - Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy*.

However, as bone scintigraphy detect tissue remodelling, as opposed to tumour burden, false positive results can be caused by inflammation, previous bone injuries, and arthritis. 18F-fluorocholine (18F-FCH) has been reported as comparably sensitive to 18F-sodium fluoride (NaF) PET for detection of bone metastases (Beheshti et al., 2010; Langsteger et al., 2011). In addition, they are not considered sufficiently sensitive methods, especially for the detection of metastases in other regions of the body (Bauman et al., 2012), and in recurrent PCa with low PSA levels (Calais et al., 2019; Evans et al., 2018; Nanni et al., 2016).

In response to this necessity to stage high-risk PCa accurately and reliably detect recurrent or metastatic disease, new prostate-specific membrane antigens (PSMAs) have been developed.

The joint guideline on diagnosis and management of prostate cancer from European Association of Urology (EAU), European Association of Nuclear Medicine (EANM), European Society for Therapeutic Radiology and Oncology (ESTRO), European Society of Urogenital Radiology (ESUR) and International Society of Geriatric Oncology (SIOG) (Mottet et al., 2022) and the latest guideline from ESMO (Parker et al., 2021) recommend that for primary staging the patients with intermediate-risk disease are staged for metastases using MRI or CT (abdomen and pelvis) and bone scan and those with high-risk disease using CT (chest, abdomen and pelvis) and bone scan. Mottet et al., state that in the primary staging "PSMA PET/CT is more accurate for staging than CT and bone scan for high-risk disease but to date no outcome data exist to inform subsequent management" (level of evidence: 1b) and that "When using PSMA PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes." (strength rating: strong). In this setting ESMO recommends not to base clinical decision-making on the outcomes of 68Ga-PSMA PET, as impact of this diagnostic tool on clinical outcomes has not been evaluated (Parker et al., 2021).

For patients with biochemically recurrent prostate cancer, PSMA-PET imaging is replacing conventional imaging, based on its superior sensitivity and specificity. (Perera et al. 2020). Nevertheless, there are no trials indicating that the earlier detection of recurrence and subsequent change in management improves outcomes. The study of modern imaging methods has focused on their diagnostic performance, not their effect on care pathways. (Perera et al., 2020; Parker et al., 2021).

2.1.5. Management

Depending on the stage (primary localised/locally advanced, recurrent PCa, metastatic/non-metastatic, etc.), patient's age (estimated life-expectancy), condition of a patient, risk profile (low-, intermediate-, high-risk PCa), etc., watchful waiting, active surveillance, or different treatment strategies (e.g., focal/systemic, definitive/palliative, surgical/non-surgical) can be utilized. Typically, in patients with primary high-risk PCa radical prostatectomy with or without lymph node dissection or radiation therapy are utilised with curative intent. However, immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) is recommended if presence of metastatic disease (M1) has been confirmed and a patient is symptomatic. ADT as part of the adjuvant therapy is also recommended after radical prostatectomy in the patients with cancer-positive lymph nodes (LN1). In the patients with suspected recurrence of PCa focal or systemic therapy options exist, including salvage radiation therapy, brachytherapy, etc., depending on the staging, type, prior treatment received, patient's condition, etc. (Mottet et al., 2022). Correct decision-making is heavily dependent on the accuracy of the diagnostic methodology used.

2.2. About the product

Piflufolastat (^{18}F) is the International Non-proprietary Name (INN) for the active substance 2-(3-(1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido) pentanedioic acid (18F-DCFPyL).

^{18}F-DCFPyL is a Glu-ureido-based, small-molecule, fluorine-18 labelled, ligand that targets the extracellular domain of PSMA with high affinity, first discovered and synthesised at the Johns Hopkins University (Ghosh and Heston, 2004).

18F-DCFPyL or piflufolastat (18F) as a ligand of PSMA, labelled with 18F, which is positron emitting and has a 109.8-minute half-life was developed as a radiopharmaceutical for use with PET.

No secondary pharmacology studies were submitted, which is acceptable. As the maximum theoretical instantaneous blood concentration is ≤18 nM, following IV administration of 18F-DCFPyL at a recommended dose of 330 MBq, the potential for off-target pharmacological effects is expected to be negligible.

^{18}F-DCFPyL injection is intended to be used as a radiopharmaceutical diagnostic agent for PCa. The injected chemical mass dose of DCFPyL in each ^{18}F-DCFPyL / piflufolastat (^{18}F) administration is a microdose of ≤40 µg, with a maximum theoretical instantaneous blood concentration of 18 nM.

In comparison with 68Ga-labelled ligands of PSMA (Calais et al., 2019; Fendler et al., 2019), 18F-DCFPyL could offer an advantage of higher production capacity and a longer half-life of Fluor-18, which

allows for wider product distribution and accessibility to patients (Werner et al., 2020; Szabo et al., 2015).

The proposed commercial formulation of 18F-DCPyL (piflufolastat (18F); Tradename: Pylclari) is a one-vial solution for injection. It is a sterile and isotonic solution, containing (18F) piflufolastat as an active substance and ethanol anhydrous, 0.9% sodium chloride and sodium ascorbate as excipients. This medicine is administered intravenously for diagnosis purpose by Position Emission Tomography (PET). Pylclari, solution for injection, is a second-generation fluorine-18-labeled small-molecule PSMA inhibitor binding PSMA.

Posology: The mean recommended activity of (^{18}F) piflufolastat is 4 MBq/kg of body weight and can vary from 3 to 5 MBq/kg of body weight depending on the PET equipment and acquisition mode used. The minimum activity should not fall below 190 MBq and the maximum activity should not exceed 360 MBq.

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, other diagnostic radiopharmaceuticals for tumour detection, ATC code: V09IX16.

2.3. Type of Application and aspects on development

A scientific advice from the EU Scientific Working Party was received on 25-July-2019 on quality, non-clinical and clinical development package. Two main clinical trials (Phase II/III – OSPREY trial and Phase III – CONDOR trial) sponsored by the applicant were presented and meant to provide key data on diagnostic efficacy, technical performance, impact on decision-making and patient management, and safety to support a marketing authorisation (MA) application. The information package provided by the applicant suggested that limited data were available on 18F-DCFPyL / piflufolastat (18F) PET/CT, and that these were likely insufficient for MA in the targeted indication, i.e. staging of high risk prostate cancer patients and localisation of locoregional recurrence, or metastatic disease. The fundamental requirement is that Phase III clinical trials consist of adequate and well-controlled data of good quality from a sufficient number of patients representative for the targeted patient population, collected by a sufficient number of investigators, demonstrating a positive benefit/risk at the intended dose and manner of use (see "Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study"; CPMP/EWP/2330/99). The presented clinical trials did not appear to fulfil these requirements. Generally, clinical relevance of the 18F-DCFPyL / piflufolastat (18F) PET-based decision-making and benefit provided by the 18F-DCFPyL / piflufolastat (18F) PET in terms of improved diagnosis/patient management will need to be discussed/addressed at the time of the application for MA.

A follow-up scientific advice from the EU Scientific Working Party was received on 12 December 2019 on clinical development package. The applicant sought confirmation that OSPREY study could be considered as comparative study fulfilling the EU guideline recommendations. The applicant sought additional confirmation of the imaging assessment method; the totality of evidence needed to establish the diagnostic efficacy; the use of the OSPREY study to support the demonstration of the benefit / risk; and the choice of the comparator.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a solution for injection containing as active substance either 1000 MBq/mL or 1500 MBq/mL of piflufolastat (^{18}F) at the date and time of calibration (that is set 1 hour after the end of the synthesis).

Other ingredients are: anhydrous ethanol, sodium ascorbate and 0.9% sodium chloride.

The product is available in type I glass vials closed with a chlorobutyl stopper and an aluminium seal as described in section 6.5 of the SmPC.

Each vial of the finished product can contain between 0.5 and 10 mL, that correspond to a total radioactivity per vial between 500 Mbq and 10,000 Mbq for the 1,000 MBq/mL strength and between 750 MBq and 15,000 Mbq for the 1,500 MBq/mL strength, expressed at calibration time.

2.4.2. Active substance ((piflufolastat (^{18}F))

As usual for PET radiopharmaceuticals containing F-18, the active substance cannot be isolated and it is synthesised and purified during the manufacture of the finished product using a non-radioactive chemical precursor as the key starting material. According to the guideline on radiopharmaceuticals, this chemical precursor should satisfy the requirements of the Note for Guidance on Summary of Requirements for Active Substances in Part II of the Dossier. Thus, the dossier includes a complete module 3.2.S. for the chemical precursor and a second module 3.2.S for the radiolabelled active substance.

General information

The proposed INN (and adopted USAN) of the active substance is piflufolastat (^{18}F) which chemical name is 2-(3-(1-carboxy-5-[(6-[^{18}F]fluoropyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid. It contains almost the same structure of the chemical precursor but with the ammonium group substituted by the radionuclide F-18 and the three carboxylic acids de-protected. The molecular formula is $C_{18}H_{23}{}^{18}FN_4O_8$. It has a relative molecular mass of 441.4 g/mol and the following structure:

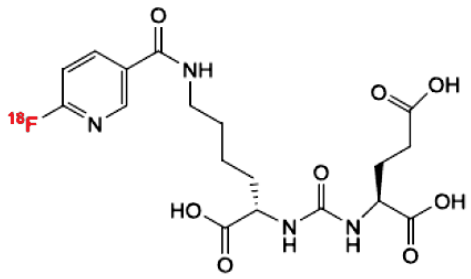


Figure 1: Active substance structure

As the active substance is synthesised with an automated unit through a continuous process leading to the finished product, without isolation of any intermediate, no structure elucidation of the active substance has been performed. All investigations performed have therefore been carried out with a nonradioactive [^{19}F]-Piflufolastat, whose structure is identical to those of [^{18}F]-Piflufolastat active substance. The structure of [^{19}F]-Piflufolastat was elucidated by FT-IR, LC-MS, and NMR

Due to the radioactive nature and the short half-life of ^{18}F of approximately 110 minutes, the ^{18}F containing [^{18}F]-Piflufolastat itself cannot be handled as an active substance. It is never isolated as such during the manufacturing process and is directly transferred into the finished product. All studies on the appearance and solubility have therefore been carried out with a nonradioactive [19F]-Piflufolastat, analogue of [^{18}F]-Piflufolastat active substance.

The active substance is a white to slightly yellow solid, solubility in solution in acetonitrile:water (1:1) is > 1 000 mg/mL.

Two chiral centers (L,L) are introduced by the L-Lysine and the L-Glutamic acid moieties. The 2 steps synthesis of the active substance (labelling and deprotection) have no impact on the chirality of the molecule, that remain unchanged from the precursor.

Manufacture, characterisation and process controls

The same sites manufacturing the finished dosage form are also the manufacturers of the radiolabelled active substance. Nine sites are proposed: Curium PET France, Sarcelles, France; Curium PET France, Janneyrias, France; Curium PET France, Pessac, France; Curium Pharma Spain, Madrid, Spain; Curium Pharma Spain, Sevilla, Spain; Curium Italy S.r.l., Milan, Italy; SYN Innovation Laboratories, Korinthia Prefecture, Greece; Argos Zyklotron Betriebs GmbH, Linz, Austria; and MAP Medical Technology Oy, Helsinki, Finland.

The manufacturing encompasses the manufacturing process starting with the production of the radionuclide, radiolabelling of the chemical precursor, hydrolysis, purification, and formulation.

The active substance is synthesised in 2 main stages: manufacture of precursor (FTNR-088) and manufacture of final active substance (([^{18}F]-DCFPyL))

Chemical Precursor (FTNR-088)

According to the Guideline on Radiopharmaceuticals, information on chemical precursors is presented in a separate section 3.2.S in Module 3.

General information (Chemical precursor)

The chemical name of the precursor is 5-(((S)-6-(tert-butoxy)-5-(3-((S)-1,5-di-tert-butoxy-1,5-dioxopentan-2-yl) ureido)-6-oxohexyl)carbamoyl)-N,N,N-trimethylpyridin-2-aminium trifluoromethanesulfonate corresponding to the molecular formula $C_{34}H_{56}F_3N_5O_{11}S$. It has a relative molecular mass of 650.84 and the following structure:

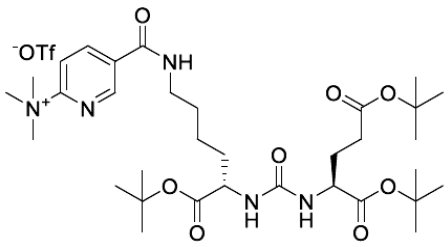


Figure 2: Chemical Precursor structure

The chemical structure of the precursor was elucidated by a combination of FT-IR, LC-MS, HR-MS and NMR.

The precursor is a white to slightly yellow solid soluble in organic solvents such as dichloromethane, ethanol, methanol and acetonitrile.

The precursor exhibits stereoisomerism due to the presence of 2 chiral centres. 100 % pure [S, S]-enantiomer is obtained.

Manufacture, characterisation and process controls (chemical precursor)

The manufacture is conducted by a single manufacturing site.

A convergent route of synthesis with two arms is used. Each arm includes three steps and the common part of the process consists in a single step. The process includes six isolated intermediates. The final purification of the chemical precursor is achieved by crystallisation in MTBE/Ethanol. The selection of starting materials is justified according to ICH Q11 and are well defined with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Evaluation of impurities was conducted according to ICH guidelines. The evaluation (using a validated HPLC method) included impurities most likely to arise during the synthesis, purification, and storage. The impurity profile was monitored at each step during the synthesis process and the data for all three process validation batches for each step. The chemical precursor has been routinely monitored for potential impurities / degradation products and residual solvents.

All impurities are controlled by specification (related substances, genotoxic impurities, residual solvents and other impurities) as per ICH guideline

Potential and actual impurities were well discussed with regards to their origin and characterised.

The precursor is packaged in a container closure system which consist of amber, Type I borosilicate screw-top glass vial and a black polyphenolic cap with PTFE liner which complies with the EC directive 2002/72/EC and EC 10/2011 as amended. Each vial is placed into an individual aluminum foil pouch and heat-sealed.

Specification (Chemical Precursor)

The chemical precursor specification includes tests for appearance (visual), identification (HPLC, IR), assay (HPLC), purity (HPLC), related substances (HPLC), elemental impurities (ICP-MS), triflate content (HPLC), chiral purity (HPLC),water content (KF), residual solvents (GC), microbial contamination (Ph. Eur.), and bacterial endotoxins (Ph. Eur.).

The European Pharmacopeia includes a general monograph for chemical precursors for radiopharmaceutical preparations. Proposed specifications include most of the tests required by this general monograph and the proposed limits are according to the compendial requirements. The test procedures are described with the required level of detail and have been validated. The limits for individual impurities and for total impurities are according to the limits prescribed in the general monograph that sets an identification threshold of 2.0% and a limit of 3.0% for total unspecified

impurities. The control strategy for residual solvents is deemed acceptable. Tests to control the microbiological quality of the chemical precursor comply with the referred general monograph on chemical precursors.

The control of the chemical precursor is satisfactory.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of 3 commercial scale batches of the chemical precursor are provided. The results are within the specifications and consistent from batch to batch.

Stability (chemical precursor)

Stability data from 3 commercial scale batches of the precursor from the proposed manufacturer stored in the intended commercial packagefor up to 60 months under long term conditions (25°C ± 2°C and 60 % ± 5 %) and for up to 12 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Additionally, stability studies are currently being conducted, on these three batches, on the bulk (before repackaging) at long-term stability study at -20°C ± 5°C for 24 months, intermediate stability study at 5°C ± 3°C for 12 months, and accelerated stability study at 25°C ± 2°C / 60 % ± 5 % RH for 6 months.

The following parameters were tested*:* appearance, identification, assay, purity, related substances, water content, microbial contamination and bacterial endotoxins.

No change and variability were observed at long-term condition and accelerated condition until 9 months either packaged or bulk.

Freeze-thaw stability study was also performed for one batch. Cycles showed no changes, hence the chemical precursor is stable during multiple freeze-thaw cycles.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 18 months after the re-packaging into the commercial container when stored at 25°C± 2°C.

Active substance ((piflufolastat (^{18}F))

The active substance is manufactured by radiolabelling of the chemical precursor using an automated synthesizer. The manufacturing process consist on 4 main steps: labelling of the precursor, hydrolysis of the intermediate, purification by demi-preparative HPLC and formulation and transfer to dispending cell A.

As the active substance is synthesised with an automated unit through a continuous process leading to the finished product, without isolation of any intermediate, the container closure system is only available for the finished product.

Specification ((piflufolastat (^{18}F))

As the active substance is synthesised with an automated unit through a continuous process leading to the finished product, without isolation of any intermediate, specifications are only available for the finished product.

Stability ((piflufolastat (^{18}F))

As the active substance is synthesised with an automated unit through a continuous process leading to the finished product, without isolation of any intermediate, stability is only available for the finished product.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as clear, colourless solution with a pH ranging from 4.5 to 7.5.

A single radioactive concentration (1000 MBq/mL at calibration time) was proposed with two alternative definitions of the calibration time (1 or 2 hours after the time of measurement of the activity of the bulk). This was not acceptable by CHMP as this would correspond to two different strengths according to the Guideline on Radiopharmaceuticals. For every batch, the calibration time should be defined at a single time point respect to the same time point of the manufacturing process. Therefore, the CHMP requested as major objection (MO) that two different strengths should be applied for. In response, the applicant applied for the two strengths and defined a single calibration time and the MO was considered satisfactorily resolved.

Development objective was to provide a parenteral formulation suitable for intravenous injection with optimum stabilization against radiolysis and high patient convenience.

Radiolabelled active substance is not isolated as such and is directly transferred into the manufacture of the finished product.

Selected excipients are commonly used for the manufacture of intravenous injections. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except 0.9 % NaCl which complies with internal monograph. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The pH of the product is controlled within the range of 4.5 to 7.5. This pH is physiologically compatible. Isotonicity is achieved by using 0.9 % NaCl solution for dilution to radioactive concentration.

Initially, a simple ethanol solution in sodium chloride was used for clinical studies. The commercial manufacturing processes was set-up to include a radio synthesis optimisation and subsequently, increased yields of radioactivity and higher radioactivity concentration led to change in the formulation composition with the addition of sodium ascorbate to reduce radiolysis.

The manufacturing of the finished product is conducted in a synthesiser. The formulation is determined by the continuous automated manufacturing process which produces the finished product.

Overall, the following improvements were made during development test campaign: increase of the uncorrected yield, removal of TFA used in the purification eluent, replaced by orthophrosphoric acid without noticeable modification of the purification conditions and limitation of the radiolysis phenomenon leading to the presence of fluorides in the final product.

The manufacturing process of the finished product was optimised first for clinical trials and also in preparation for commercial manufacturing to increase the yield and robustness. The manufacture of the finished product corresponds to the dilution to 1 000 or 1 500 MBq/mL at calibration time, sterilisation of the finished product by filtration on a 0.22 µm membrane taking place at the dispensing step. Dilution and dispensing are performed in a shielded isolator equipped with laminar air flow

equipment providing a class A. The manufacturing process gives a low bioburden prior to sterile filtration and the aseptic dispensing process is validated at each manufacturing site.

To evaluate of the bioburden prior to sterilising filtration, a bioburden test is performed on the bulk solution during the validation process studies. Apart from the aseptic processing inherent to the production of sterile parenteral finished products (controlled environment, pre-sterilized materials and pre-sterilized-equipment in a clean area), the microbiological safety of the manufacturing process is favoured by several process parameters like short process duration that limit the risk of microbial growth. In addition, radioactivity is also known for its anti-microbial effect. The sterilizing filtration step provides an additional guarantee to the microbiological safety of the manufacturing process.

Two kind of sterilising-filters membrane (Polyethersulfone - PES and Mixed Cellulose Ester - MCE) were validate and used through the process validation studies performed at each manufacturing sites leading to sterile finished product batches. Additionally, for each sterilising filter, the minimum bubble point value was established to confirm the use of the supplier's specification as routine specification limit for the filter integrity test. The final sterile filtration step of the manufacturing is crucial for the quality of the finished product. Consequently, the integrity of the sterile filter is regarded as critical and tested as process control.

Finished product batches of are subject to testing for sterility and endotoxins as part of the finished product specification. Due to the short shelf-life the results of sterility testing will only be available after release for use of the finished product.

The process validation and stability studies and experience with manufacture have confirmed the compatibility of the finished product with sterile 0.9 % sodium chloride solution. As regards to batch analysis results and stability data obtained for all validation batches, all tested parameters, comply with specifications for 11 hours. All the results obtained for the validation batches comply with the specifications. The compatibility of the finished product with sterile 0.9 % sodium chloride solution is thus demonstrated.

The results of the leachables and extractable tests have been provided and are deemed satisfactory.

The primary packaging is type I glass vials closed with a chlorobutyl stopper and an aluminium seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by 9 manufacturing sites.

The manufacturing process consists of 5 continuous main steps, steps 1 to 4 corresponding to the manufacture of the active substance (see above) and step 5 corresponding to the manufacture of the finished product consisting of a dilution for radioactive concentration adjustment, sterilisation, filling an sealing. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. Validation reports cover the complete manufacturing process, including the manufacture of the radiolabelled active substance and the subsequent dilution to target concentrations and aseptic filling into the final vials. This validation approach is satisfactory and provided results would support the suitability of the process as it is proposed. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (gamma ray spectrometry, gamma ray spectrometry or ionization chamber, HPLC,), pH (Ph. Eur.), radionuclidic purity (Ph. Eur., gamma ray spectrometry), radiochemical purity (HPLC, TLC), chemical purity (HPLC, spot test, strip test), residual solvents (GC), bacterial endotoxins (Ph. Eur.), sterility (direct inoculation.), and radioactive concentration (Ph. Eur., ionisation chamber).

Proposed specifications for batch release comply with the minimum requirements of the general Ph. Eur. monograph 0125 (Radiopharmaceutical preparations). The test procedures are described with the required level of detail and validation data is provided. Each test and proposed limits are justified.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for six validation batches manufactured at each site batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 batches per strength manufactured on each manufacturing site of finished product stored for up to 11 hours after End of Synthesis under long term conditions (25 ºC / 60% RH) and under accelerated conditions (40 ºC / 75% RH) in upside-down position, according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Moreover, multidose stability studies were also performed for each container-closure system (different manufacturers) respectively strength at 1 000 MBq/mL and 1 500 MBq/mL. The vials were stored at 40°C ±2°C in upside-down position until expiry time of the drug product, i.e. 11 hours after End of Synthesis.

Additionally, four complementary validation batches have been performed with the highest starting activities.

Samples were tested for appearance, identification, pH, radiochemical purity and chemical purity.

As regards to batch analysis results obtained for the batches from all manufacturing sites, all tested parameters comply with the shelf-life specifications during the 11 hours study duration when stored upside-down at 25 ± 2°C and/or 40 ± 2°C for both minimum and maximum filled volumes.

As regards to batch analysis results obtained for multidose stability study, all tested parameters comply with the specifications during the 11 hours study duration when packaged in multidose vials stored at 40 ± 2°C for all container closure system manufacturers.

Thus, the finished product does not require any special storage conditions and can be packaged in multidose vials.

Based on available stability data, the proposed shelf-life of 11 hours from the end of manufacturing as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the assessment the CHMP requested the application of two defined strength(s) at a single defined calibration time instead one strengths according to the Guideline on Radiopharmaceuticals instead of one strength with two calibration times. The applicant amended the expression of strength and calibration time in line with the CHMP's requested and it was considered satisfactory.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

The primary pharmacology, pharmacokinetics, as well as PET imaging data of piflufolastat (18F) were investigated *in vitro*, *ex vivo* and *in vivo* in mouse xenograft models and are described in the literature. An extended single dose toxicity GLP study evaluating the toxicity of DCFPyL on Days 3 and 15

following a single IV dose in rats (report SB-MP001) was submitted. Further to the scientific advice from CHMP/SAWP received on 25 July 2019, the applicant also submitted results from *in silico* evaluation of potential mutagenicity of piflufolastat (18F).

2.5.2. Pharmacology

Information presented in this section is based on data from Chen et al. (2011) and Roy et al. (2021).

2.5.2.1. Primary pharmacodynamic studies

18F-DCFPyL is a novel urea-based, small molecule ligand of PSMA labelled with the widely available isotope fluorine-18. Urea based, low molecular weight ligands of Glutamate carboxypeptidase II (GCPII) were shown to bind strongly to the active site of PSMA, as shown by X-ray crystallography studies (Barinka et al., 2008) and have been shown to be internalised into the cell following ligand binding (Ghosh and Heston, 2004; Kiess et al., 2015).

Published non-clinical pharmacology studies were presented to provide support for the recommended dose of ^{18}F-DCFPyL of 330 MBq (9 mCi), administered by intravenous (IV) injection, as a PET imaging agent to patients with high risk, recurrent, or metastatic PCa. Formal *in vitro* and *in vivo* pharmacodynamics studies were not submitted by the applicant.

Primary pharmacology was investigated *in vitro* using an enzyme-inhibition assay and *in vivo* in small animal PET imaging studies. DCFPyL was observed to bind competitively to PSMA expressing lymph node carcinoma of the prostate (LNCaP) cells with an inhibition constant (Ki) of 1.1 nM. 18F-DCFPyL showing high affinity binding (dissociation constant (Kd)=0.83±0.04 nM) to PSMA and high specific binding (85–98 %). 18F-DCFPyL showed PSMA-dependent uptake within PSMA-positive PC3 PIP[1] xenografts, reaching a value of 46.7±5.8% ID/g at 30 minutes post injection, which decreased by only about 10% over the ensuing 4 hours. The ratio of uptake within PSMA-positive to PSMA-negative tumours ranged from 40:1 to more than 1000:1 over the 4-hour time period of the study.

The results showed significant uptake and retention in the PSMA positive tumour, and a rapid clearance from non-target organs (Roy et al., 2021).

2.5.2.2. Secondary pharmacodynamic studies

No data were presented which was considered acceptable by the CHMP (see discussion on non-clinical aspects).

2.5.2.3. Safety pharmacology programme

No data were presented which was considered acceptable by the CHMP (see discussion on non-clinical aspects).

[1] PC3 cells transfected with PSMA

2.5.2.4. Pharmacodynamic drug interactions

No data were presented which was considered acceptable by the CHMP (see discussion on non-clinical aspects).

2.5.3. Pharmacokinetics

Formal *in vitro* and *in vivo* pharmacokinetics and metabolism studies were not submitted by the applicant. The pharmacokinetics and biodistribution of 18F-DCFPyL were assessed based on the data from a published study by Chen et al. (2011), as shown in Table 4.

Table 1. Pharmacokinetics Studies with ^{18}F-DCFPyL / piflufolastat (18F)

Type of Study	Test System	Method of Administration	Testing Facility	Study Number
Pharmacokinetics	NOD-SCID Xenograft Mice (n=4 each time point)	IV	Johns Hopkins University	Chen et al., 2011
Distribution	NOD-SCID Xenograft Mice (n=4 each time point)	IV	Johns Hopkins University	Chen et al., 2011
Metabolism	Not conducted	–	–	–
Excretion	Not conducted	–	–	–

IV=intravenous; NOD=nonobese diabetic SCID=severe combined immunodeficiency disease.

In a PSMA-positive PC3 PIP mouse xenograft study, clear PSMA-dependent uptake within tumours was observed, reaching a value of 46.7±5.8%ID/g at 30 minutes post injection and decreased by only about 10% over the ensuing 4 hours. The normal organ demonstrating the highest uptake was the kidney, with a value of 74.1±6.6%ID/g at 30 minutes but clearing rapidly down to 7.4±0.9%ID/g at 4 hours. Using the mouse biodistribution data from this study, the human radiation dosimetry values were estimated. The organ with the highest mean absorbed dose per unit administered activity was the urinary bladder wall, 0.15 mGy/MBq, followed by the kidneys at 0.05 mGy/MBq. The critical dose limit of 50 mGy was set in reference to the FDA Code of Federal Regulations, Title 21, part 361.1 (Radioactive drugs for certain research uses). As the bladder wall was considered the limiting organ (0.15 mGy/MBq), the maximal dose in MBq that could be administered was 50/0.15 = 333 MBq.

The actual human dosimetry data (from Szabo et al. 2015), obtained from 4 patients with prostate cancer, showed that the absorbed doses were in the same ranges as those estimated from the mouse data. Similarly, the effective dose from [18F]DCFPyL determined from human data was 0.0165 mSv/MBq or 6.1 mGy (0.61 rem) for an injected dose of 370 MBq (10 mCi) which was similar to that estimated from the mouse data. The organs with the highest absorbed radiation dose were estimated for the kidneys (0.0945 mGy/MBq) followed by urinary bladder wall (0.0864 mGy/MBq). These organs were similarly identified using the mouse data as those receiving the highest absorbed dose (although the bladder wall was higher than the kidney based on the mouse data). Based on the critical dose limit of 50 mGy, the maximal dose in MBq that could be administered using the kidney 0.0945 mGy/MBq was 50/0.0945= 529 MBq (higher than the value 333 MBq estimated using the mouse data).

Data from a biodistribution study in mice showed rapid and high uptake in the kidney, as well as extensive bladder exposure, following IV injection of F-DCFPyL (Table 4; Chen et al., 2011), suggesting a urinary clearance for F-DCFPyL in mice. Indeed, in a phase 1 study by Szabo et al. (2015), 18F-DCFPyL did not appear to undergo meaningful metabolism. Coupled with the concomitant high uptakes in the kidney and bladder, further support that 18F-DCFPyL / piflufolastat (18F) is renally excreted following IV administration in men with PCa.

No pharmacokinetic drug interaction studies were submitted.

2.5.4. Toxicology

Table 2: Toxicology Studies with DCFPyL

Study Type and Duration	**Species and Strain**	**Route of Admin.**	**Test Article Doses (mg/kg)**	**Study Number**	**GLP Status**
Extended Single Dose Toxicity with 14-day Observation period	Rat, Sprague Dawley	I.V.	DCFPyL 0, 0.1, 0.5	SBMP-001	yes
Repeat-Dose Toxicity	None	-	-	-	-
Genotoxicity	None	-	-	-	-

2.5.4.1. Single dose toxicity

The potential toxicity of DCFPyL (non-radioactive) after a single dose administration was evaluated in a GLP-compliant extended single-dose toxicity study conducted in male and female Sprague Dawley rats with intravenous administration. Male and female Sprague Dawley rats were assigned to 6 groups (n=5/gender/group) and dosed IV on Day 1 with 0.1 or 0.5 mg/kg DCFPyL or vehicle control. Assessment of toxicity was based on mortality, clinical signs, body weight, body weight changes, and clinical and anatomic pathology.

This study revealed no adverse effects up to the highest tested dose, 0.5 mg/kg, which is significantly higher than the estimated dose of the non-radioactive part to be administered to patients.

Dosing solutions at 0.02 and 0.1 mg/mL were higher than the concentrations seen clinically (max clinical concentration 4µg/mL) and the rat volume/kg is far greater than the clinical volume (0.16 mL/kg for a 60 kg patient). In the rat study the injection site was monitored during the observation phase (dosing day through day 3 and 15) of the study and also during physical examination on the day of weighing. No indication of any tail/injection site irritation was noted.

Injection sites were collected during animal necropsy, which was an integral part of the study protocol. Five animals per sex per group were sacrificed on day 3 post-dose and 5/sex/group were sacrificed on day 15 post-dose.

No adverse reactions were observed in any of the animals, and no deaths occurred at the highest tested dose of 0.5 mg/kg. This dose is over 875-fold higher than the maximum clinical dose of 40

µg/patient (or 0.5714 µg/kg for a reference body weight of 70 kg); on a body surface area basis, this dose is approximately 142-fold higher, suggesting adequate safety margin.

2.5.4.2. Repeat dose toxicity

No repeated dose toxicity studies have been submitted.

2.5.4.3. Genotoxicity

A predictive toxicology study for the assessment of DNA reactivity (mutagenicity) using expert rule-based and statistical-based (Q)SAR prediction methodology was submitted. An *in silico* computational evaluation of 18F-DCFPyL was performed using DEREK Nexus, an expert knowledge-based tool and Sarah Nexus, a statistical-based tool.

In Derek Nexus, the test item structure was imported through or developed in the software. Possible alerts fire in Derek because toxicophores in the processed structures match alerts in the knowledge base. Therefore, reasoning considers evidence outlined in a Derek Nexus predefined set of rules to provide a logical outcome. Similarly, in Sarah Nexus, the test item was also imported through its developed structure in the software in which the query test item was virtually fragmented. Each fragment was then assessed for generation of relevant hypotheses (i.e., fragments not out of domain) to generate hypothesis, signal, confidence and supporting examples. An overall prediction was the combination of both the prediction and the confidence. The mutagenic potential of 18F-DCFPyL was evaluated using both systems. As per results from Derek and Sarah reports, the 18F-DCFPyL was within the domain of application of the model. The parameters that have influenced the Derek Nexus prediction were the substructures in the input structure, which have a potential for mutagenicity, in the selected species, which is bacterium, i.e., the Ames' test.

The Derek prediction indicated that the structure did not match any structural alerts or examples for the bacterial *in vitro* mutagenicity and that the structure did not contain any unclassified and misclassified features. As such, there were no features that were not found following a search in the reference set (data from public domain) and that the features were found in non-alerting mutagens in the reference set, respectively. The compound was predicted to be negative with 36% confidence for the 'Mutagenicity' endpoint in the Sarah methodology.

2.5.4.4. Carcinogenicity

No carcinogenicity studies were submitted (see discussion on non-clinical aspects).

2.5.4.5. Reproductive and developmental toxicity

No reproductive toxicity studies were submitted (see discussion on non-clinical aspects).

2.5.4.6. Toxicokinetic data

No other studies than an extended single-dose toxicity study were submitted. See 2.5.4.1.

2.5.4.7. Local Tolerance

Consistent with the ICH guideline M3(R2) (Dec 2009) a formal local tolerance study was not performed as the mass of drug is very low (40µg max; microdose) and no novel vehicles are used. Information is however available from the single dose extended toxicity study performed in rats with iv injection. See 2.5.4.1.

All injection site tissue was recorded as appearing visually normal. Injection site (tail vein) histopathology evaluation showed 2/5 male and 2/5 female day 3 control rats had grade 1 perivascular mixed inflammatory infiltration of the injection site. Similarly,1/5 male and 1/5 female rats day 3 rats treated with 0.1 mg/mL (0.5mg/kg) DCFPyL had grade 1 perivascular mixed inflammatory infiltration of the injection site. Both control and 0.1 mg/mL (0.5 mg/kg) DCFPyL day 15 female and male rats injection sites had no abnormal findings.

2.5.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) of (18F) DCFPyL CURIUM (Pylclari) solution for injection, 1000 MBq/mL was performed according to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use EMEA/CHMP/SWP/4447/00 corr 2, 2006, and the Question and Answers document of the same Guideline (EMA/CHMP/SWP/44609/2010 Rev.1, 2016).

Table 3. Summary of main study results

Substance (INN/Invented Name): (18F) DCFPyL CURIUM			
CAS-number (if available): 601721			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-0.92	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-0.92	not B
	BCF		not B
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		PECsw Refined = 0.00000009µg/L	> 0.01 threshold N

2.5.6. Discussion on non-clinical aspects

The extended single-dose toxicity study revealed no adverse effects up to the highest tested dose, 0.5 mg/kg, which is significantly higher than the estimated dose of the non-radioactive part to be

administered to patients.

An issue has been identified regarding the choice of the control group in the extended single-dose toxicity study - control animals received 5% Dextrose solution, while this does not correspond to the vehicle used for the test article. The applicant was, therefore, asked to justify for the choice of the control group and discuss possible impact on the interpretation of the results of the study. In response, the applicant claimed that there was no impact on the interpretation of the results from the study. This was because neither the vehicle for the DCFPyL (0.9% sodium chloride) nor the 5% Dextrose administered to control animals provoke adverse reactions/toxicity and, in the extended single-dose toxicity study, no adverse reaction/toxicity signals were observed in the DCFPyL treated groups. A clear justification for the choice of the control group was not provided. Considering the results from the extended single-dose toxicity study and the large safety margins, the issue on the choice of the control group is not pursued.

The lack of repeated dose toxicity and reproductive toxicity studies is accepted considering the intended use of (18F) DCFPyL CURIUM and current guidelines. (18F) DCFPyL CURIUM is to be used as a diagnostic agent, with administration of a dose corresponding to not more than 40 µg of the non-radioactive part of radiopharmaceutical.

Non-clinical findings suggest that there is no concern regarding local tolerance for DCFPyL even when administered at much higher concentrations and volume/kg than present in clinical doses. This conclusion is also supported by human safety data, where no issues were identified with the local tolerance of [18F]-DCFpyL injection. Additionally, no literature data, suggesting any safety concern regarding injection site reactions related to the use of [18F]DCFPyL was identified.

Taken together, the submitted data on primary pharmacodynamics provided adequate pharmacology support for the development of 18F-DCFPyL as a diagnostic agent for the detection of PCa.

(^{18}F) DCFPyL CURIUM, solution for injection is a microdose diagnostic agent which is administered at a low mass dose of ≤40 µg. It is highly selective to PSMA. The selectivity and the very low chemical mass in an administered dose renders any meaningful interaction with off target receptors, transporter, and ion channels, including hERG (human Ether-à-go-go-Related Gene) potassium channel, highly unlikely (Guideline on the non-clinical requirements for radiopharmaceuticals EMA/CHMP/SWP/686140/2018; European Medicines Agency (EMA). ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals Step 5 EMA/CPMP/ICH/286/1995, December 2009). No secondary pharmacology studies were submitted, which is acceptable. As the maximum theoretical instantaneous blood concentration is ≤18 nM, following IV administration of 18F-DCFPyL at a recommended dose of 330 MBq, the potential for off-target pharmacological effects is expected to be negligible.

No safety pharmacology studies were submitted, which is acceptable. According to EMA, "Guideline on the non-clinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018), safety pharmacology studies for radiopharmaceutical diagnostic agents are not required. Based on the same rationale than above, the interaction of 18F-DCFPyLwith PSMA is unlikely to result in any clinically significant pharmacological or toxicological activity to result in any safety concern.

No pharmacodynamic drug interactions studies and no secondary pharmacodynamic drug interactions were submitted. The maximum chemical mass of DCFPyL associated with the recommended dose of 330 MBq is ⩽40 µg. At such low chemical dose, DCFPyL is not expected to produce any meaningful pharmacologic effect, and the potential for pharmacodynamic interactions of 18F-DCFPyL with concomitant drugs is negligible.

Formal in vitro and in vivo pharmacokinetics and metabolism studies were not submitted by the applicant. The pharmacokinetics and biodistribution of 18F-DCFPyL were assessed based on the data

from a published study by Chen et al. (2011). This study performed in an animal model of disease, is considered adequate, as the tracer was shown to possess high in vivo stability and underwent basically no metabolic transformation after distribution.

The methods of analysis developed at the Johns Hopkins University study (Chen et al. (2011)), based on the measurement of radioactivity concentrations in blood and tissues in mice, is considered adequate, as all counted samples were inside the linearity range established during operational qualification of the F-18 counting method. A relatively low bone uptake of ^{18}F-DCFPyL radioactivity (<1%ID/g at all time points) suggested a low potential for metabolic de-fluorination of ^{18}F-DCFPyL in mice. In accordance, Szabo et al. (2015) reported no metabolism of ^{18}F-DCFPyL was observed on radioHPLC analysis following IV administration in humans, thus, provided further support that it is not necessary to conduct metabolism studies in animals.

The high kidney uptake (the mouse biodistribution data (chen et al., 2011)), coupled with extensive bladder exposure, suggested a renal clearance of 18FDCFPyL. Additionally, a relatively low bone uptake of 18F-DCFPyL radioactivity (<1%ID/g at all time points) suggested a low potential for metabolic de-fluorination of 18F-DCFPyL in mice. Furthermore, Szabo et al. (2015) reported no metabolism of 18F-DCFPyL was observed on radioHPLC analysis following IV administration in humans.

As ^{18}F-DCFPyL does not undergo meaningful metabolism following IV administration in humans, and considering the low mass dose administered, it is agreed that it is unnecessary to evaluate DCFPyL as an inhibitor or inducer of metabolic enzymes or transporters.

No pharmacokinetic drug interaction studies were submitted. The extremely low mass dose is highly unlikely to inhibit or induce any of the metabolizing enzymes. Furthermore, since ^{18}F-DCFPyL / piflufolastat (18F) does not undergo meaningful metabolism following IV administration in humans (Szabo et al., 2015), its pharmacokinetics would not be affected by concomitant inducers and/or inhibitors of metabolising enzymes. Taken together, the potential for meaningful ^{18}F-DCFPyL / piflufolastat (18F) pharmacokinetic drug interactions is negligible and the absence of PK drug interactions studies is considered acceptable.

The potential toxicity of DCFPyL (non-radioactive) after a single dose administration was evaluated in a GLP-compliant extended single-dose toxicity study conducted in male and female rats with intravenous administration. No adverse effects were identified up to the highest tested dose, 0.5 mg/kg, which is significantly higher than the estimated dose of the non-radioactive part to be administered to patients.

No repeated dose toxicity studies and no reproductive studies were submitted which is considered acceptable taking into account the intended use of Pylclari and current guidelines. Pylclari is to be used as a diagnostic agent, with administration of a dose corresponding to not more than 40 µg of the non-radioactive part of radiopharmaceutical.

Regarding the genotoxicity assessment, given that both complementary computational methodologies support the same conclusion, it is considered that 18F-DCFPYL is expected to be devoid of mutagenic hazard as could be assessed by the Ames' test. The methodology of the predictive toxicology study for the assessment of DNA reactivity (mutagenicity) was adequately validated, according to the data provided in the study report. 18F-DCFPYL can be categorized in Class 5 ("No structural alerts or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity") and no further testing is recommended following ICH M7 (2017). This product is to be treated as non-mutagenic. This is endorsed and in agreement with the scientific advice provided by CHMP.

No carcinogenicity studies nor reproductive toxicity studies were submitted, no further justifications were provided but, given the intended use (e.g. the therapeutic indication) and the currently available scientific guidance, this is considered to be acceptable.

Based on EMA "Guidelines on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018)" (EMA, 2018) and "Nonclinical safety studies for the conduct of human clinical trials and Marketing Authorisation (EMA/CPMP/ICH/286/1995)" (EMA, 2009), and US FDA guidance "Microdose radiopharmaceutical diagnostic drugs: Nonclinical study recommendations; Guidance for industry, 2018" (CDER, 2018), developmental and reproductive toxicity studies are not necessary because of the inherent radiation risk to the foetus from the radiopharmaceutical drug, which would be reflected in labelling.

The justifications for the lack of dose formulation analysis for concentration, homogeneity, stability, and toxicokinetic analysis are essentially related to the nature of the formulation (a "true solution", with a "very straight forward preparation") and to the intravenous route of administration. Considering the large safety margins, even if there were minimal inaccuracies and/or losses of the test article during the preparation procedure and dosing of the animals, these are not expected to be able to significantly impact the results.

For drugs used at microdose levels in single dose extended toxicity studies the drug should be used by intended route of administration with toxicokinetic data, or via the i.v. route (ICH guideline M3(R2) (Dec 2009). In this case the drug solution was administered by intravenous route, wherein the drug preparation was deposited directly into the circulation the entire amount of the drug is available in the body for distribution, metabolism, pharmaco- toxicological actions and ultimate elimination. Thus, while safety margin based on Cmax or AUC are not available, two dose levels were evaluated with drug solution administered IV and the lack of toxicokinetic information is not considered to have impacted on the reliability of the study.

It also has to be emphasized that the study procedure took into consideration a very large safety margin. The highest tested dose of 0.5 mg/kg is over 875-fold higher than the maximum clinical dose of 40 µg/patient (or 0.5714 µg/kg for a reference body weight of 70 kg); on a body surface area basis, this dose is approximately 142x higher. Therefore, even if there were minimal inaccuracies and/or losses of the test article during the preparation procedure and dosing of the animals, these are not expected to be able to significantly impact the results.

According to the available guidance, investigation of local tolerance, where applicable, should be done as integral part of the extended single dose study, Data suggested that there is no concern regarding local tolerance for DCFPyL even when administered at much higher concentrations and volume/kg than present in clinical doses. This conclusion is also supported by human safety data, where no issues were identified with the local tolerance of [18F]-DCFpyL injection. Additionally, no literature data, suggesting any safety concern regarding injection site reactions related to the use of [18F]DCFPyL was identified.

Pylclari solution for injection Refined PEC $_{surfacewater}$ value is below the action limit of 0.01 µg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5. A further screening for persistence, bioaccumulation and toxicity (PBT assessment) is deemed not necessary.

Therefore, Pylclari is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the nonclinical data package presented to support the application for Pylclari, solution for injection is considered satisfactory.

2.6. Clinical aspects

2.6.1. Introduction

Progenics has conducted a clinical development program in North America to support de use of 18F-DCFPyL as a PET imaging radiopharmaceutical for the detection of PCa.

Two US studies (OSPREY and CONDOR) were conducted in North America and Canada to assess the safety and efficacy of 18F-DCFPyL injection in patients with high risk and those with recurrent or metastatic PCa.

More recently, Progenics/Lantheus contracted a partnership with Curium in order to conduct a clinical development program in Europe, PYTHON study.

GCP aspects

The clinical study (PYTHON) conducted in the EU was performed in accordance with good clinical practice (GCP) as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 4. Tabular overview of clinical studies

Type of Study Clinical Phase	Study No. Study reference.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Numbers of Subjects	Healthy Subjects Or Diagnosis of Patients
PK Phase II/III	PyL2301 NCT02981368	Pharmacokinetics, biodistribution and excretion	Open-label	333 (± 37) MBq Single IV injection	10	Patients with high-risk localized prostate cancer
Efficacy/ safety Phase II/III	PyL2301 NCT02981368 OSPREY	• To assess the diagnostic performance of 18F-DCFPyL PET/CT imaging to: o determine the presence or absence of metastatic disease in pre-prostatectomy patients with high-risk PCa. o determine the presence or absence of PCa within sites of metastasis or local recurrence. • Detection rate, PPV, NPV • Safety and tolerability	Prospective, open-label, multi-reader	333 (± 37) MBq Single IV injection	385 (268 in Arm A, 117 in Arm B)	Patients with at least high-risk PCa (Arm A) and patients with new or progressive metastatic disease or radiologic evidence of local recurrence (Arm B)
Efficacy/ safety Phase III	PyL3301 NCT03739684 CONDOR	• To determine the Correct Localization Rate (CLR) of 18F-DCFPyL PET/CT imaging in the detection of recurrent PCa at the patient level.	Open-label, single-arm, non-randomized, multi-reader	333 MBq Single IV injection	208	Recurrent PCa with negative or equivocal findings per institutional standard of care conventional imaging.

		• To assess the impact of 18FDCFPyL PET/CT disease detection on patient's clinical management plans. • Safety and tolerability				
Efficacy/ Safety Phase III	PYTHON 2020-000121-37	o To compare per-patient detection rate of 18F-DCFPyL PET/CT versus that of 18F-FCH PET/CT o To assess impact on patient treatment/ management. o To compare per-region detection rate of 18F-DCFPyL PET/CT versus that of 18F-FCH PET/CT. o Sensitivity and specificity of 18F-DCFPyL PET/CT versus that of 18F-FCH PET/CT on a per-patient and per-region basis, using a composite SOR. o To assess concordance rate between 18F-DCFPyL PET/CT and 18F-FCH PET/CT for regions using a composite SOR. o Safety of 18F-DCFPyL versus that of 18F-FCH	Prospective, open label, cross-over, randomized, central image evaluation	330 MBq ± 10% Single IV injection	205	First biochemical recurrence of PCa

2.6.2. Clinical pharmacology

Clinical pharmacology studies of 18F-DCFPyL were conducted as sub-studies in OSPREY (PyL2301), where male subjects with high risk localized prostate cancer scheduled to undergo radical prostatectomy (RP) with pelvic lymph node dissection (PLND), or presumptive recurrent or metastatic prostate cancer on conventional imaging, were administered with a single IV dose of 18F-DCFPyL at 333 MBq. The following clinical pharmacology topics were investigated:

• PK/distribution/disposition/ metabolite profiling/excretion, including effects of renal status on PK (10 subjects in cohort A of the study – PK cohort)

• Normal organ dosimetry (PK cohort, N=10)

• Impact of renal function on diagnostic performance (all subjects in study, N=385)

• Cardiovascular safety evaluation (all subjects in study, N=385) o 12-lead electrocardiograms (ECG) at pre-dose and pre-imaging

2.6.2.1. Pharmacokinetics

Absorption

- Bioavailability

Not applicable: Pylclari is administered intravenously. Consequently, the absolute bioavailability is 100%.

- Influence of food

On empirical grounds, the 4- to 6-hours fast has often been recommended (Li X, Rowe SP, Leal JP, et al. Semiquantitative parameters in PSMA-targeted PET imaging with 18F-DCFPyL: variability in normal-organ uptake. J Nucl Med.2017;58:942–946) before a patient undergoes PET/CT with 18F DCFPyL; however, a scientific underpinning for this recommendation is lacking. Wondergem et al. (2018) performed a study to determine the impact of fasting on 18F-DCFPyL in 50 patients who fasted at least 6 hours before administration and 50 patients who did not.

Overall, these data showed that fasting did not significantly affect 18F-DCFPyL uptake in suspected malignant lesions but did result in significantly lower 18F-DCFPyL uptake in tissues with high physiologic uptake.

- Bioequivalence

A single formulation of 18F-DCFPyL drug product has been used in the clinical studies.

Biodistribution

A pharmacokinetic (PK) cohort of 10 subjects was included in Study PyL2301 (OSPREY) to determine the pharmacokinetics, biodistribution, and excretion of 18F-DCFPyL, including metabolic profile in urine.

Ten (10) subjects with high risk localized prostate cancer scheduled to undergo radical prostatectomy with pelvic lymph node dissection **(cohort A) in Study PyL2301** were enrolled. One subject had normal

kidney function at screening (eGFR≥90 mL/min/1.73m^2) while the other nine subjects had mild kidney insufficiency (60<eGFR<90). Each patient received a single intravenous injection of 18F-DCFPyLat a target level of 333 MBq.

Blood, urine and whole-body PET/CT scans were to be collected at the timelines noted in Table 8.

Table 5. PK Sampling & Imaging Timepoints

Procedure	Pre-dose	0 hr	5±2 m	15± 2 m	30± 5 m	1± 0.25 hr	2± 0.25 hr	3± 0.25 hr	4± 0.25 hr	6± 0.25 hr	8± 0.25 hr
^{18}F-DCFPyL Administration		X									
Blood & Plasma Collection	X		X	X	X	X	X		X	X	X
Urine Collection		<----------X---------->					<-----X---->		<------X------>		
^{18}F-DCFPyL PET/CT Imaging		X				X			X		

Analytical Methods

Gamma counting method

The gamma counting method used for measuring the radioactivity concentrations at specific time points, after the administration of 18F-DCFPyL to ten patients in the PK cohort of study PyL2301, was based on a publication by Lodge et al. (2015).

Blood, plasma, and urine were collected and counted in an automated γ-counter that consisted of a single 75-mm-diameter, 80-mm-high NaI (Tl) crystal with a 33-mm-diameter, 60-mm-deep hole. The detector was surrounded by 50 to 75 mm of lead shielding. The dead time correction efficacy, background correction accuracy, sample volume, and counting efficiency were optimized for Fluorine-18.

Batch counting was done for the samples collected between 0 and 4, at 6, and at 8 hours post-injection. Radioactivity of all counted samples was within the linearity range established during operational qualification of the Fluorine-18 counting method. The raw radioactivity counts were converted into radioactivity concentrations (µCi/mL) using an appropriately diluted aliquot of 18F-DCFPyL drug product as a reference standard. All resulting radioactivity concentrations were decay-corrected to the time of administration.

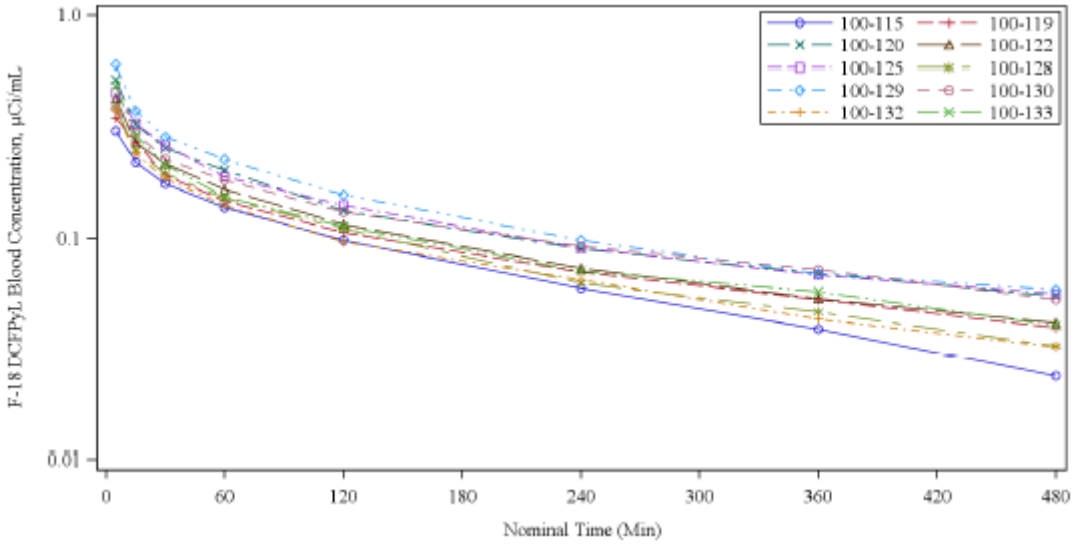
HPLC/Radiometric method

The HPLC/radiometric detection method used to determine the metabolic profile in urine, following administration of 18F-DCFPyL to ten patients in the PK cohort of study PyL2301 study, was based on a publication by Szabo et al. (2015). The chromatographic separation was achieved on Gemini 4.6×250 mm C18 column with an isocratic elution using 10% acetonitrile/90% triethylammonium phosphate (pH 3.2) mobile phase at a flow rate of 2 mL/min.

- Distribution

The graph of 18F-DCFPyL blood concentrations vs. time is depicted in Figure 3. All values are expressed as the mean ± standard deviation (SD).

Figure 3: ^{18}FDCFPyL Blood Concentrations vs. Time



After the intravenous administration of 18F-DCFPyL, the blood levels rapidly declined in a biphasic fashion. The half-life of the alpha (distribution) portion of the curve was 0.17 ± 0.044 hours with the beta (elimination) half-life of 3.47 ± 0.490 hour.

The terminal elimination phase was reliably established in two out of ten subjects resulting in half-life of 3.33 ± 0.348 hour.

The effective half-life of piflufolastat (^{18}F) is approximately 70 minutes.

The duration of the observation period in the study, however, was limited by a short decay half-life of the radioisotope (F-18, 110 minutes).

Table 6: Summary of 18F-DCFPyL Blood Pharmacokinetics in Ten Subjects with Prostate Cancer

Subject	C_{max} (µCi/mL)	AUC_{inf} (h*µCi/mL)	AUC_{last} (h*µCi/mL)	CL (mL/h/kg)	V_{ss} (mL/kg)	MRT (h)	$t_{1/2\ elim}$ (h)	$t_{1/2\ alpha}$ (h)	$t_{1/2\ beta}$ (h)	Kidney Function
1	0.306	0.719	0.615	128.227	502.878	3.922	3.084	0.161	2.732	Normal
2	0.350	1.013*	0.738	75.783*	457.774*	6.041*	4.848*	0.244	3.986	Mild Insufficiency
3	0.518	1.372*	0.932	93.723*	646.685*	6.900*	5.568*	0.122	3.652	Mild Insufficiency
4	0.430	1.071*	0.783	86.153*	507.975*	5.896*	4.809*	0.140	3.218	Mild Insufficiency
5	0.455	1.419*	0.985	85.706*	573.766*	6.695*	5.363*	0.200	3.803	Mild Insufficiency
6	0.392	0.888*	0.709	104.353*	489.485*	4.691*	3.816*	0.138	2.883	Mild Insufficiency
7	0.602	1.494*	1.047	75.504*	485.938*	6.436*	5.295*	0.166	3.411	Mild Insufficiency
8	0.388	1.250*	0.904	79.413*	475.754*	5.991*	4.521*	0.249	4.286	Mild Insufficiency
9	0.378	0.838	0.672	125.014	576.362	4.610	3.577	0.151	3.140	Mild Insufficiency
10	0.487	1.044*	0.799	97.170*	517.145*	5.322*	4.206*	0.151	3.611	Mild Insufficiency
N	10	2	10	2	2	2	2	10	10	
Mean (SD)	0.43 (0.088)	0.78 (0.084)	0.82 (0.143)	126.62 (2.272)	539.62 (51.961)	4.27 (0.487)	3.33 (0.348)	0.17 (0.044)	3.47 (0.490)	
Geom. Mean	0.42	0.78	0.81	126.61	538.37	4.25	3.32	0.17	3.44	
Median	0.41	0.78	0.79	126.62	539.62	4.27	3.33	0.16	3.51	
Min, Max	0.3, 0.6	0.7, 0.8	0.6, 1.0	125.0, 128.2	502.9, 576.4	3.9, 4.6	3.1, 3.6	0.1, 0.2	2.7, 4.3	
CV%	20.32	10.77	17.43	1.79	9.63	11.41	10.46	25.66	14.12	

*- in this subject, the adjusted $R^2 > 0.8$ but the extrapolated portion of AUCinf exceeded 20% of the total area; the calculated derived parameter may not be accurate and should be interpreted with caution; value is not included in summary statistic

As listed in Table 10, the plasma-to-blood concentration ratios at any time-point for all subjects were between 1.441 and 1.829, indicating 18F-DCFPyL exhibited a restricted permeability into red blood cells (RBCs) (ratio of 1 corresponds to equal distribution between plasma and RBCs while ratio of 2 signifies a complete lack of permeability).

Table 7: Ratios of Plasma-to-Blood Concentrations per Subject/Time-point in 10 subjects

Subject	Nominal time-point, minutes							
	5	15	30	60	120	240	360	480
1	1.602	1.568	1.547	1.590	1.531	1.556	1.581	1.645
2	1.642	1.624	1.647	1.641	1.708	1.696	1.711	1.730
3	1.441	1.578	1.605	1.714	1.677	1.659	1.581	1.529
4	1.633	1.625	1.640	1.618	1.674	1.656	1.599	1.464
5	1.624	1.561	1.579	1.627	1.630	1.596	1.639	1.569
6	1.642	1.577	1.605	1.671	1.601	1.679	1.706	1.656
7	1.696	1.684	1.637	1.712	1.757	1.775	1.702	1.522
8	1.678	1.620	1.651	1.700	1.680	1.727	1.612	1.644
9	1.681	1.683	1.613	1.735	1.731	1.722	1.829	1.817
10	1.726	1.705	1.683	1.731	1.736	1.805	1.631	1.739

Accumulation

Organ uptake

Physiologic accumulation of piflufolastat (^{18}F) was observed in the kidneys (16.5% of administered activity), liver (9.3%), and lung (2.9%), within 60 minutes of intravenous administration. Most of the remaining 70% of activity at 60 minutes was with the rest of the body background region.

Radiation Dosimetry

Selection of Clinical Dose and Optimal Imaging Timepoint

Prior to the first-in-human study with 18F-DCFPyL at the Johns Hopkins University (JHU), human dosimetry was extrapolated from a preclinical biodistribution study in xenograft mice. The urinary bladder wall was projected to be the organ with the highest absorbed dose. To limit the radiation-absorbed dose to the urinary bladder, the highest human dose was estimated to be 331.2 MBq.

The results of PK, metabolism, excretion, dosimetry, and safety evaluations from the first-in human study at JHU were reported by Szabo et al. Physiologic accumulation of 18F-DCFPyL was shown to correspond to the distribution of PSMA-expressing organs. Outside of the tumour, the longest residence time in normal organs was observed in kidneys, liver, muscle, and bladder.

The effective dose from an injected dose of 333 MBq 18F-DCFPyL, calculated to be 0.0169 mSy/MBq or 5.5 mGy (0.55 rem), was comparable to that of other radiotracers used in oncology, such as 18F-fluorodeoxyglucose. Therefore, a dosage of 18F-DCFPyL Injection of 333 MBq was selected for use in the phase 2/3 trial, OSPREY, and the phase 3 study, CONDOR.

In the Szabo et al. study, the highest uptake and lowest background activity were observed at approximately 1 and 2 hours, respectively, suggesting that the optimal imaging time point following injection of 18F-DCFPyL could be 1-hour post injection. Therefore, PET/CT imaging was to be initiated 1 to 2 hours after 18F-DCFPyL administration.

Although no formal administered dose finding studies of 18F-DCFPyL were performed by investigators at Johns Hopkins University (JHU) as part of the first-in-man study of this novel PSMA tracer, the dose of 333 MBq was deliberately selected to be in line with both the ALARA principle and current 18F-FDG dose recommendations.

Normal organ dosimetry

Serial PET/CT images were collected in the 10 subjects of the PK cohort of study PyL2301 (OSPREY) at 10 minutes, and 1- and 4-hours post-injection (times are nominal).

Activity concentrations for selected tissues/organs including time-integrated activity coefficients and clearance rates, and radiation absorbed dose estimates were calculated following three consecutive PET/CT images for each subject.

The absorbed radiation doses per tissue/patient are listed in Table 11.

For all 10 patients, kidney was the organ with the highest absorbed dose. The mean effective dose to the whole body from 18F-DCFPyL was calculated to be 0.0116 mSv/MBq or 3.9 mGy (0.39 rem) for an injected dose of 333 MBq which is less than other commonly used tracers for oncologic imaging such as 18F-FDG.

Table 8: Absorbed doses (mGy/MBq) per organ of the individual patients in PK cohort

Organ	Subject										Average*	SD*
	1	2	3	4	5	6	7	8	9	10		
Adrenals	1.20E-02	1.30E-02	1.26E-02	1.52E-02	1.27E-02	1.19E-02	1.45E-02	1.41E-02	1.66E-02	1.11E-02	1.31E-02	1.30E-03
Brain	2.15E-03	1.43E-03	2.11E-03	2.02E-03	2.25E-03	1.87E-03	2.30E-03	2.51E-03	2.28E-03	1.76E-03	2.07E-03	3.12E-04
Breasts	6.25E-03	4.53E-03	6.09E-03	5.91E-03	6.11E-03	5.43E-03	5.49E-03	6.78E-03	6.44E-03	4.85E-03	5.75E-03	6.80E-04
Gall bladder Wall	1.34E-02	1.37E-02	1.34E-02	1.62E-02	1.41E-02	1.42E-02	1.38E-02	1.59E-02	1.51E-02	1.19E-02	1.41E-02	1.24E-03
LLI Wall	8.10E-03	5.63E-03	7.73E-03	7.47E-03	7.99E-03	6.67E-03	7.09E-03	8.73E-03	8.12E-03	6.14E-03	7.34E-03	9.56E-04
Small Intestine	9.21E-03	7.47E-03	9.02E-03	9.45E-03	9.31E-03	8.06E-03	8.93E-03	1.02E-02	1.01E-02	7.45E-03	8.85E-03	9.06E-04
Stomach Wall	9.33E-03	7.95E-03	9.56E-03	9.87E-03	9.37E-03	8.77E-03	9.55E-03	1.04E-02	1.38E-02	7.70E-03	9.21E-03	8.41E-04
ULI Wall	9.39E-03	7.80E-03	9.19E-03	9.79E-03	9.53E-03	8.45E-03	9.08E-03	1.05E-02	1.02E-02	7.65E-03	9.10E-03	8.94E-04
Heart Wall	1.94E-02	1.45E-02	1.94E-02	1.64E-02	1.39E-02	1.58E-02	1.70E-02	1.56E-02	2.04E-02	1.96E-02	1.71E-02	2.21E-03
Kidneys	7.35E-02	1.66E-01	9.86E-02	1.72E-01	9.78E-02	6.98E-02	1.91E-01	9.99E-02	1.55E-01	1.09E-01	1.23E-01	4.34E-02
Liver	3.27E-02	3.99E-02	3.22E-02	4.53E-02	3.58E-02	4.51E-02	3.13E-02	4.27E-02	3.46E-02	3.12E-02	3.70E-02	5.76E-03
Lungs	9.88E-03	7.83E-03	1.27E-02	1.06E-02	9.35E-03	9.67E-03	1.07E-02	1.16E-02	1.28E-02	7.85E-03	1.02E-02	1.61E-03
Muscle	7.30E-03	5.57E-03	7.13E-03	7.17E-03	7.28E-03	6.34E-03	6.76E-03	8.01E-03	7.93E-03	5.75E-03	6.86E-03	7.61E-04
Ovaries	8.52E-03	6.10E-03	8.16E-03	8.02E-03	8.45E-03	7.11E-03	7.56E-03	9.24E-03	8.55E-03	6.54E-03	7.80E-03	9.70E-04
Pancreas	1.17E-02	1.16E-02	1.25E-02	1.39E-02	1.21E-02	1.20E-02	1.34E-02	1.35E-02	2.03E-02	1.04E-02	1.24E-02	1.05E-03
Red Marrow	7.22E-03	5.98E-03	7.21E-03	7.53E-03	7.34E-03	6.35E-03	7.22E-03	8.09E-03	8.23E-03	6.01E-03	7.06E-03	7.09E-04
Osteogenic Cells	1.08E-02	7.69E-03	1.04E-02	1.01E-02	1.07E-02	9.06E-03	9.57E-03	1.17E-02	1.10E-02	8.32E-03	9.89E-03	1.23E-03
Skin	5.59E-03	4.06E-03	5.38E-03	5.31E-03	5.54E-03	4.75E-03	4.98E-03	6.08E-03	5.75E-03	4.31E-03	5.15E-03	6.21E-04
Spleen	2.04E-02	2.32E-02	4.19E-02	2.48E-02	1.67E-02	4.68E-02	4.04E-02	2.44E-02	2.46E-01	1.64E-02	2.71E-02*	1.15E-02
Testes	6.61E-03	4.35E-03	6.24E-03	5.88E-03	6.48E-03	5.36E-03	5.54E-03	7.07E-03	6.29E-03	4.90E-03	5.87E-03	8.34E-04
Thymus	7.67E-03	5.39E-03	7.45E-03	7.07E-03	7.39E-03	6.49E-03	6.65E-03	8.17E-03	7.68E-03	5.96E-03	6.97E-03	8.45E-04
Thyroid	6.92E-03	4.59E-03	6.58E-03	6.19E-03	6.77E-03	5.66E-03	5.84E-03	7.42E-03	6.66E-03	5.16E-03	6.17E-03	8.63E-04
Urinary Bladder Wall	7.98E-03	5.40E-03	7.56E-03	7.23E-03	7.85E-03	6.55E-03	6.80E-03	8.58E-03	7.72E-03	5.98E-03	7.16E-03	9.74E-04
Uterus	8.59E-03	6.09E-03	8.21E-03	8.03E-03	8.50E-03	7.14E-03	7.57E-03	9.29E-03	8.57E-03	6.56E-03	7.83E-03	9.89E-04
Eff Dose (mSv/MBq)	1.08E-02	1.17E-02	1.03E-02	1.38E-02	1.14E-02	9.98E-03	9.94E-03	1.27E-02	1.29E-02	1.00E-02	1.16E-02	2.21E-03

*based on an average of N=9 patients (subject 9) was excluded as considered to be an outlier with a spleen value approximately 10-times higher)

Dosimetry

Data listed below are from sponsored clinical studies (i.e. 10 subjects of the PK cohort of study PyL2301 (OSPREY).

Assumptions:

Fluorine (^{18}F) decays to stable oxygen (^{18}O) with a half-life of 110 minutes by emitting a positronic radiation of maximum energy of 634 keV, followed by photonic annihilation radiations of 511 keV.

Piflufolastat (^{18}F) exhibits bi-exponential behaviour in blood, with a distribution half-life of 0.17 ± 0.044 hours and an elimination half-life of 3.47 ± 0.49 hours. It distributes to the kidneys (16.5% of administered activity), liver (9.3%), and lung (2.9%), within 60 minutes of intravenous administration.

Methodology:

The time-integrated activity in source tissue was obtained from longitudinal imaging data. Contours or volumes of interest (VOIs) were typically drawn around different activity-containing organs that were identified on each image at each time-point. The S-value was obtained by Monte Carlo simulation. The absorbed doses calculation was performed on OLINDA/EXM software (2005). The resulting effective dose was calculated according to ICRP 60.

ORGAN	ABSORBED DOSE PER UNIT ACTIVITY ADMINISTERED (mGy/MBq)
Adrenals	0.0131
Bone surfaces	0.0099
Brain	0.0021
Breast	0.0058
Gallbladder wall	0.0141
Gastrointestinal tract	
Stomach wall	0.0092
Small Intestine wall	0.0089
Upper large intestine wall	0.0091
Lower Large Intestine wall	0.0073
Heart wall	0.0171
Kidneys	0.123
Liver	0.037
Lungs	0.0102
Muscles	0.0069
Pancreas	0.0124
Red marrow	0.0071
Skin	0.0052
Spleen	0.0271
Testes	0.0059
Thymus	0.007
Thyroid	0.0062
Urinary bladder wall	0.0072
Effective dose (mSv/MBq)	**0.0116**

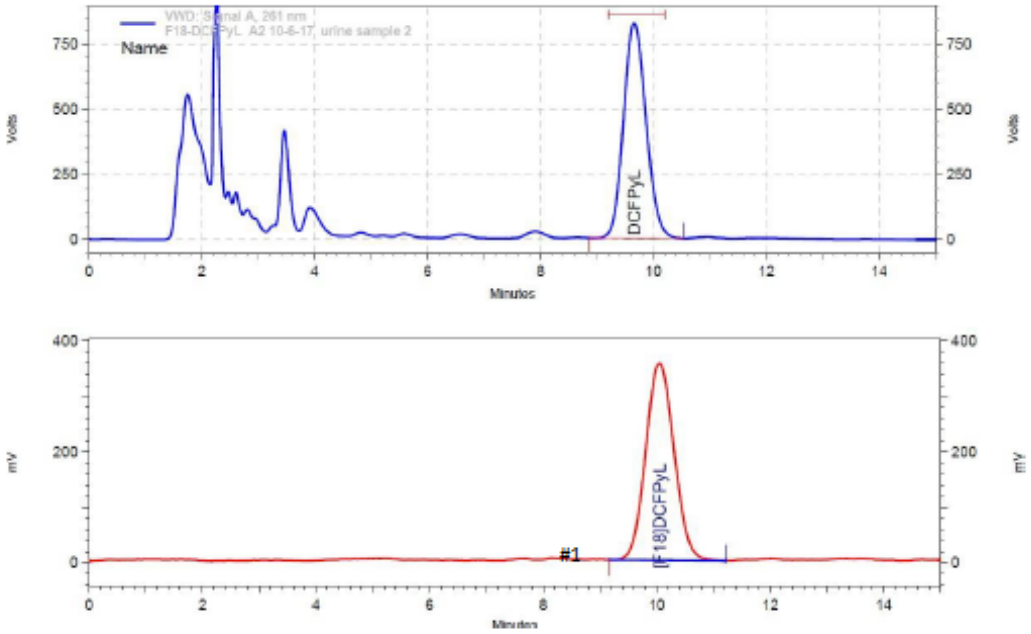
The effective dose resulting from the administration of a maximal recommended activity of 360 MBq for an adult weighing 70 kg is about 4.2 mSv.

For an administered activity of 360 MBq, the typical radiation doses to the critical organs (kidneys, liver and spleen) are 44.3 mGy, 13.3 mGy and 9.8 mGy respectively.

Metabolism

Analysis of urine samples by high-performance liquid chromatography (HPLC) collected up to 8 hours post-injection demonstrated that in nine subjects all urine activities at all three collection intervals were in the form of unmetabolized parent compound (**Figure 4**)

Figure 4. Typical Metabolic Profile of 18F-DCFPyL in Urine (HPLC analysis with UV and Radio-Detector) Observed in 9 out of 10 Subjects.

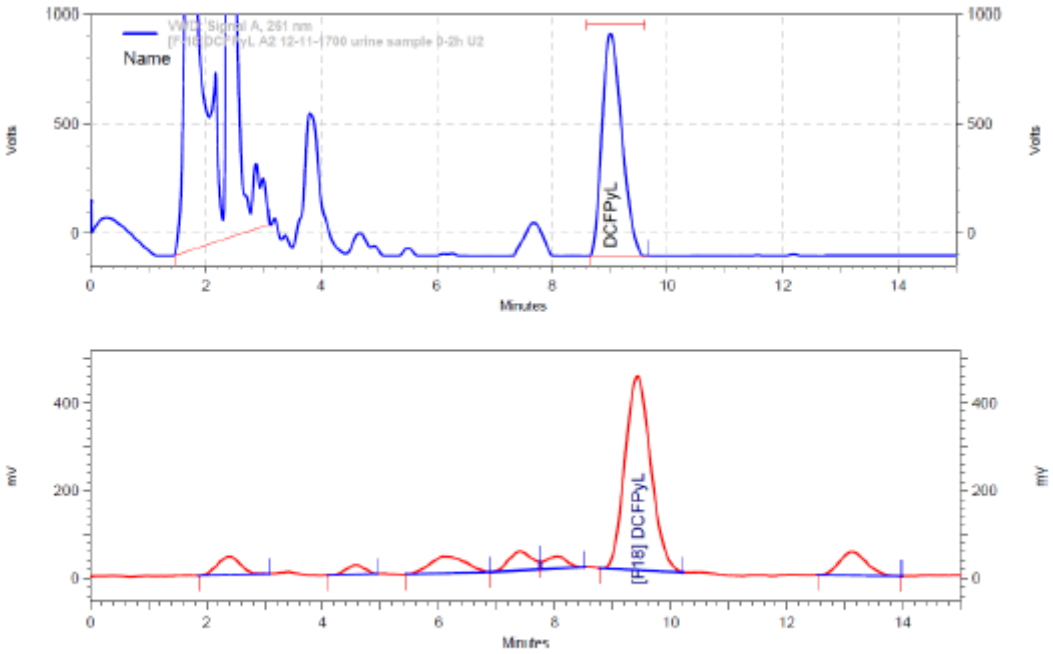


HPLC analysis of 0-2 hours urine collection, subject . #1 · sample was spiked with cold DCFPyL reference standard; upper trace (blue)- UV; lower trace (red)- radio-detector

For 1 Subject (subject #4 in the above tables), 0-2 hours urine collection interval contained 1.7% of injected activity. The unmetabolized 18F-DCFPyL eluted at 9.4 minutes (

Figure 5 below) representing 66.3% of the total peak area on a radio-chromatogram. The other peaks of potential minor metabolites eluted at 2.4, 4.6, 6.1, 7.4, 8.0, and 13.1 minutes each representing 2.2 to 8.6 % of the total peak area.

Figure 5. Metabolic Profile of 18F-DCFPyL in Urine of Subject #4 Collected 0-2 hours Post-dose



Sample was spiked with cold DCFPyL reference standard; upper trace (blue)- UV; lower trace (red)- radio-detector

Elimination

18F-DCFPyL was rapidly cleared via the kidney with the most rapid rate of 848.97 ± 236.807 µCi/hr. By 8 hours post injection, 50.09 ± 7.616 % of the ID (decay-corrected) was present in the urine (Table 12). All values are expressed as the mean ± standard deviation (SD).

Table 9. Summary of 18F-DCFPyL Urinary Kinetics in Ten Subjects with Prostate Cancer

Subject	T_{max} (h)	Rate Max (µCi/h)	Rate Last (µCi/h)	%ID Cumulative Urine Recovery (0-8 h)	Baseline eGFR (mL/min/1.73m^2)	Kidney Function
1	3	1022.874	594.144	57.445	99.063	Normal
2	3	659.587	615.469	50.353	67.043	Mild Insufficiency
3	3	643.011	363.247	40.954	82.488	Mild Insufficiency
4	3	929.137	418.313	40.243	69.723	Mild Insufficiency
5	1	780.346	498.172	49.285	72.845	Mild Insufficiency
6	3	1369.902	194.172	48.846	84.206	Mild Insufficiency
7	3	914.964	509.017	63.112	86.075	Mild Insufficiency
8	6	524.760	524.760	41.768	61.546	Mild Insufficiency
9	3	785.151	628.391	56.511	75.229	Mild Insufficiency
10	1	860.015	417.281	52.372	73.246	Mild Insufficiency
N	10	10	10	10		
Mean (SD)	2.9 (1.37)	848.97 (236.807)	476.30 (133.128)	50.09 (7.616)		
Geom. Mean	2.6	821.33	454.54	49.57		
Median	3.0	822.58	503.59	49.82		
Min, Max	1, 6	524.8, 1369.9	194.2, 628.4	40.2, 63.1		
CV%	47.3	27.89	27.95	15.21		

Amount of injected activity (%ID) remaining in the body by 4 h post-dose for each subject was derived

from the serial PET/CT images. Together with the cumulative urine recovery (0-4 hours), the data established that urinary excretion was the predominant elimination route of ^{18}FDCFPyL (Table 13). In the first 8 hours post-injection, approximately 50% of administered radioactivity was excreted in the urine.

Table 10. Disposition of the Injected Dose (decay-corrected) by 4 Hours Post-Dose

Subject	%ID Cumulative Urine Recovery (0-4 h)	% Activity Remaining in the Body by 4 Hours
1	32.4	82.96
2	24.1	73.91
3	25.6	66.05
4	22.0	86.56
5	27.5	59.38
6	40.8	65.73
7	40.2	58.12
8	18.6	87.17
9	27.2	79.57
10	34.2	66.57
MEAN	**29.3**	**72.60**

The only radioactive component detected in plasma samples by high-performance liquid chromatography (HPLC) up to 173 minutes post-injection was unchanged piflufolastat (^{18}F).

Special populations

- **Impaired renal function**

The pharmacokinetics in patients with renal impairment has not been characterised.

A formal analysis was conducted to assess the effects of renal function (normal, mild, and moderate) vs. diagnostic performance (sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for patients in cohort A; and sensitivity and PPV for patients in cohort B).

Table 11. Diagnostic Performance of 18F-DCFPyL PET/CT for Pelvic Lymph Nodes by Baseline Renal Function (Cohort A Evaluable Set)

Renal impairment (eGFR)	Reader	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Normal eGFR≥90, N=63	1	47.1 (23.3, 70.8)	100 (90.8, 100)*	100 (62.8, 100)*	83.6 (73.9, 93.4)
	2	35.3 (12.6, 58.0)	100 (90.8, 100)*	100 (55.7, 100)*	80.7 (70.5, 91.0)
	3	41.2 (17.8, 64.6)	95.7 (84.7, 99.6)*	77.8 (44.3, 94.7)*	81.5 (71.1, 91.8)
Mild 60≤eGFR<90 , N=169	1	38.1 (23.4, 52.8)	97.6 (93.0, 99.5)*	84.2 (61.6, 95.3)*	82.7 (76.6, 88.7)
	2	28.6 (14.9, 42.2)	99.2 (95.2, 100)*	92.3 (64.6, 100)*	80.8 (74.6, 87.0)
	3	35.7 (21.2, 50.2)	96.1 (90.9, 98.6)*	75.0 (52.8, 89.2)*	81.9 (75.7, 88.1)
Moderate 30≤eGFR<60 , N=16	1	66.7 (20.2, 94.4)*	100 (73.4, 100)*	100 (29.0, 100)*	92.9 (66.5, 100)*
	2	33.3 (5.6, 79.8)*	100 (73.4, 100)*	100 (16.8, 100)*	86.7 (60.9, 97.5)*
	3	100 (38.3, 100)*	100 (73.4, 100)*	100 (38.3, 100)*	100 (38.3, 100)*

The Evaluable Set for Cohort A consists of all dosed patients who received a prostatectomy or lymphadenectomy; patients must have a ^{18}F-DCFPyL PET imaging result and a corresponding histology result.
In general, 2-sided 95% CIs were derived from a one-sample binomial distribution.
* two-sided 95% CIs were derived using Agresti-Coull method.

Table 12. Sensitivity and PPV of 18F-DCFPyL PET/CT in Recurrent or Metastatic Prostate Cancer by Baseline Renal Function (Cohort B Evaluable Set)

Renal Impairment (eGFR)[a]	Reader	Sensitivity (%)	PPV (%)
Normal (eGFR≥ 90) N=30	1	100 (82.5, 100)[b]	81.5 (62.8, 92.3)[b]
	2	100 (82.5, 100) [b]	81.5(62.8, 92.3)[b]
	3	95.5 (76.5, 100)[b]	80.8 (61.7, 91.9)[b]
Mild (60≤ eGFR<90) N=49	1	100 (88.5, 100)[b]	78.3 (66.3, 90.2)[a]
	2	91.7 (77.4, 97.9)[b]	78.6 (66.2, 91.0) [a]
	3	94.4 (80.9, 99.4)[b]	91.9 (78.0, 97.4)[b]
Moderate (30≤ eGFR<60) N=12	1	90.9 (60.1,100)[b]	90.9 (60.1, 100)[b]
	2	100 (71.8, 100)[b]	92.3 (64.6, 100)[b]
	3	81.8 (51.2,96.0)[b]	90.0 (57.4, 100)[b]

The Evaluable Set for Cohort B includes all patients who received a conventional image guided biopsy; these patients must have a 18F-DCFPyL PET imaging result and a corresponding histology result.
NOTE: One patient from cohort B with severe renal impairment (eGFR <30) was not included in the table. The patient had a positive 18F-DCFPyL PET/CT finding (all 3 readers) and histopathology (patient = True Positive).
[a] Two-sided 95% CIs were derived from a one-sample binomial distribution.
[b] Two-sided 95% CIs were derived using Agresti-Coull method.

- ***Impaired hepatic function***

The pharmacokinetics in patients with hepatic impairment has not been characterised.

- ***Gender***

There was no investigation in women, as the proposed indication is not intended for women.

- ***Race***

The pharmacokinetics in different races has not been characterised.

- ***Weight***

An analysis of the potential impact of body weight on exposure has not been performed.

- ***Elderly***

	<65 years	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK cohort	7/10	2/10	1/10	0/10

- ***Children***

There was no investigation in children as the proposed indication is not intended for children. Pursuant to Article 13 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0357/2019) on the granting of a product-specific waiver for (18F) piflufolastat (EMA-002608-PIP01-19).

Pharmacokinetic interaction studies

Androgen Deprivation therapies

While there was no concomitant use of androgen deprivation therapy (ADT) in patients enrolled in CONDOR, 55 patients (26.4%) had prior treatment with ADT. No difference was observed in the correct localisation rate (CLR) of 18F-DCFPyL in patients previously treated with ADT compared with those without prior treatment.

In OSPREY Cohort B, one-third of the patients (32 out of 93) had concurrent ADT use, which was defined as medications with start dates prior to and ongoing at 18F-DCFPyL injection dosing. A post-hoc analysis on the effect of concomitant use of ADT on the efficacy of 18F-DCFPyL in the OSPREY Cohort B patients concluded to no difference in sensitivity or PPV in patients who received concomitant ADT when compared to patients without ADT use.

Diuretics

There were 20/252 (7.9%) evaluable patients in OSPREY Cohort A identified as concurrent diuretic users. In OSPREY Cohort B, there were 15/93 (16.1%), and in CONDOR there were 24/208 (11.5%) evaluable patients identified with concurrent diuretic use.

2.6.2.2. Pharmacodynamics

Mechanism of action

Prostate-Specific Membrane Antigen (PSMA), is a trans-membrane glycoprotein primarily expressed in normal human prostate epithelium at low levels, but may be overexpressed by malignant tissues, particularly by prostate cancer cells, including metastatic disease. Fluorine (^{18}F) is a β+ emitting radionuclide that enables positron emission tomography. Piflufolastat (^{18}F) is a selective second-generation fluorine-18-labeled small-molecule PSMA inhibitor. Based on the intensity of the signals, PET images obtained using piflufolastat (^{18}F) indicate the presence of PSMA expressing tissues.

Primary and Secondary pharmacology

A 12-lead electrocardiogram (ECG) was collected in a total of 374 study subjects in OSPREY at 2 intervals on the day of study drug administration: pre-dose (Baseline) and prior to imaging.

Baseline and change from Baseline in mean and median QTc values are presented in Table 16. No clinically relevant changes were observed between the pre-dose and pre-imaging time points.

Table 13. Summary and Change from Baseline in QTc Interval (Safety Set)

ECG Parameter Time Point Statistic	Cohort A		Cohort B		Overall	
	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline
QTcF (msec)						
Baseline	N=260		N=114		N=374	
Mean (SD)	406.3 (20.00)	–	418.7 (23.97)	–	410.1 (22.01)	–
Pre-Imaging						
Mean (SD)	408.3 (19.88)	1.9 (10.21)	421.5 (24.82)	2.6 (9.68)	412.3 (22.31)	2.1 (10.04)
QTcB (msec)						
Baseline	N=260		N=114		N=374	
Mean (SD)	413.9 (22.92)	–	427.3 (25.10)	–	418.0 (24.38)	–
Post-PyL Dosing						
Mean (SD)	412.8 (22.28)	-1.3 (12.57)	427.2 (27.17)	-0.3 (12.92)	417.1 (24.74)	-1.0 (12.67)

QTcB = QT interval corrected with Bazett's formula; QTcF = QT interval corrected with Fridericia's formula; SD = standard deviation.

2.6.3. Discussion on clinical pharmacology

The clinical pharmacology properties of 18F-DCFPyL for the detection of macroscopic lesions of prostate cancer have been characterized using information from the pharmacokinetic cohort of 10 subjects in Study OSPREY (cohort A). Pharmacokinetics studies have not been conducted in healthy subjects following the recommendation of the 97/43/EURATOM Directive regarding the use of radioactive drugs only in subjects with a direct benefit.

Absorption

18F-DCFPyL is administered intravenously and therefore 100% bioavailable. The same formulation was used during the clinical development; consequently, there are no possible differences in excipients that could interact with the drug substance. Therefore, no comparative bioavailability or bioequivalence studies were required. With regards to the influence of food in tissues uptake of DCFPyL, as the absolute differences in uptake between patients who fasted and patients who did not were relatively small, the effects of fasting on the diagnostic performance of Pylclari can be considered negligible.

Distribution

18F-DCFPyL is rapidly and extensively distributed following an IV dose with a distribution half-life (T 1/2 alpha) of 0.17 ± 0.044 hours and steady state Volume of distribution (Vss) of 539.62 ± 51.961 mL/kg. Furthermore, 18F-DCFPyL exhibits a restricted permeability into red blood cells (RBCs).

Since the terminal elimination phase was not reliably established in eight out of ten subjects, the derived pharmacokinetics parameters calculated using non-compartmental model in those subjects (denoted with asterisk in Table 9) may not be accurate and should be interpreted with caution.

Normal organ dosimetry

According to the effective dose (0.0116 mSv/MBq) a recommended clinical dose of 333 MBq of 18F-DCFPyL results in 3.9 mSv, a value comparable to the radiation effective dose of other Fluorine-18

radiopharmaceuticals such as ^{18}F-FDG (0.019 mSv/MBq). The table containing the average of effective dose has been calculated according to the ICRP Publication 60 (1991). In view if a potential optimisation of the benefit risk balance, the effective dose will be updated post-approval according to the most recent ICRP Publication 103, 2007. New generation softwares that use anthropomorphic and biokinetic models for absorbed doses calculations as OLINDA/EXM version 2.0 or IDAC-Dose 2.1 should be used and the version number of the software should be included in the section 11 of the SmPC (**REC**).

Elimination

18F-DCFPyL is mainly excreted through urine. Data showed that approximately 50% of the administered radioactivity was eliminated by 8 hours post injection.

Analysis of urine samples by HPLC collected up to 8 hours post dose demonstrated that 18F-DCFPyL does not undergo meaningful metabolism following IV administration. Only one subject showed potential minor metabolites.

Impaired renal function

The pharmacokinetics in patients with renal impairment has not been characterised (see SmPC section 5.2). Data from the subgroup analysis in Osprey study showed that diagnostic performance was not different when comparing patients with normal renal function to patients with mild renal impairment. However, the pharmacokinetics of 18F-DCFPyL was studied only in 10 patients, 1 with normal kidney function at screening (eGFR $\geq$ 90) and 9 subjects with mild kidney insufficiency (60< eGFR<90). Therefore, PK profile was mainly established for mild kidney insufficiency patients. For all 10 patients, kidney was the organ with the highest absorbed dose. The mean effective dose to the whole body from piflufolastat (18F) was calculated to be 0.0116 mSv/MBq or 3.9 mSv for an injected dose of 330 MBq. In patients with moderate or severe renal impairment, slower excretion of piflufolastat (18F) is expected, and the mean residence time will be increased. There are no data on radiation dose resulting from administration of piflufolastat (18F) in those patients. Given the low micro-dose and short effective half-life of approximately one hour (70 min), moderate or severe renal impairment was regarded unlikely to have a clinical impact on PK or biodistribution of piflufolastat (18F) with respect to safety or the imaging performance and no dose adjustment is proposed for patients with renal impairment. Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible (see SmPC section 4.2 and 4.4).

Impaired hepatic function

The pharmacokinetics in patients with hepatic impairment has not been characterised (see SmPC section 5.2). 18F-DCFPyL is mainly eliminated by urinary excretion. In addition, 18F-DCFPyL does not seem to undergo meaningful metabolism. In this sense, liver function is not expected to affect 18F-DCFPyL disposition.

Pharmacokinetics interactions

No dedicated drug interaction study were submitted. Due to the extreme low chemical mass in an administered dose of 18F-DCFPyL, meaningful interactions with metabolizing enzymes, transporters or ion channels are highly unlikely. In addition, 18F-DCFPyL does not undergo a meaningful metabolism, indicating that blood concentrations of 18F-DCFPyL is not expected to alter in the presence of concomitant inducer or inhibitor drug.

Available data did not show differences in sensitivity or positive predictive value (PPV) in patients who received concomitant Androgen Deprivation Therapies (ADT) compared to patients who did not use ADT. No special recommendation is provided regarding the concomitant use of ADT. Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor

antagonists, may result in changes in uptake of piflufolastat (^{18}F) in prostate cancer. The effect of these therapies on performance of piflufolastat (^{18}F) PET has not been established (see SmPC section 4.5).

The use of diuretics at the time of administration of 18F-DCFPyL did not appear to impact the diagnostic performance of 18F-DCFPyL injection in newly diagnosed PCa patients or patients with recurrent or metastatic disease. Chronic treatment with diuretics does not seem to have any interference with piflufolastat (^{18}F) for interpretation of images (see SmPC section 4.5). However, these analyses need to be interpreted with caution due to small number of patients in certain cohorts and due to the post-hoc nature of these analyses.

Pharmacodynamics

At the chemical concentrations used for diagnostic examinations, this medicinal product does not appear to have any pharmacodynamic activity because the injected mass is negligible (less than 40 µg).

A 12-lead electrocardiogram (ECG) was collected in a total of 374 study subjects in OSPREY (safety set). The results showed no clinically relevant changes in QTc values between the pre-dose and pre-imaging time points, suggesting the potential of cardiovascular risk from 18F-DCFPyL injection is minimal. In addition, 18F-DCFPyL is a microdose radiopharmaceutical diagnostic agent with the maximum administered chemical dose of $\leq$ 40 micrograms and maximum theoretical instantaneous blood concentration is 18nM. The very low chemical mass in an administered dose of 18F-DCFPyL renders any meaningful interactions with ion channels (e.g., hERG) highly unlikely. The results suggest that 18F-DCFPyL administration is not linked to changes in QTc prolongation.

2.6.4. Conclusions on clinical pharmacology

In conclusion, the clinical pharmacology of piflufolastat (^{18}F) has been adequately characterized and the rationale for the dosing is considered appropriate. Based on the available data, no dose adjustment is required in older patients, in patients with renal impairment or in patients with hepatic impairment. However, careful consideration of the benefit risk ratio in patients with renal impairment is required since an increased radiation exposure is possible. No clinically significant interactions with other medicinal products are expected.

In order to optimize the B/R, dosimetry will be re-calculated with new generation software and updated in accordance with ICRP Publication 103, 2007 (**REC**).

2.6.5. Clinical efficacy

This radiopharmaceutical is intended for the detection of prostate-specific membrane antigen (PSMA) positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings (1) Primary staging of patients with high-risk PCa prior to initial curative therapy (2) To localize recurrence of PCa in patients with a suspected recurrence based on increasing serum prostate-specific antigen (PSA) levels after primary treatment with curative intent.

The submitted dossier consists of a full mixed MAA based on three studies OSPREY (PyL2301, NCT02981368), CONDOR (PyL3301, NCT03739684), PYTHON (EudraCT number 2020-000121-37), (Table 17) and on available bibliographic data (Table 18).

Table 14: Description of Clinical Studies

Protocol	**OSPREY** (PyL2301–NCT02981368)	**CONDOR** (PyL3301, NCT03739684)	**PYTHON** (EudraCT number 2020-000121-37)
Study Start-End Date	30 November 2016–19 July 2018	30 November 2018–29 August 2019	01 July 2020–17 December 2020
Number of Centres	US: 8 sites Canada: 2 sites	US: 13 sites Canada: 1 site	EU: 22 sites (France, Spain, Belgium, Netherlands)
Study Design	Multicentre, phase 2/3, open-label, nonrandomised, controlled study	Multicentre, phase 3, open-label, single-arm, nonrandomised, controlled study	Multicentre, phase 3, open-label, cross-over, randomised, controlled study
Dose Regimen and Route **PET Imaging**	333±37 MBq as a single IV injection; PET/CT imaging initiated 1-2 hours following drug dosing	333 MBq±20% as a single IV injection; PET/CT imaging initiated 1-2 hours following drug dosing	321.2 MBq (range 186.9-373) as a single IV injection, PET/CT initiated 120 (range 80- 150) minutes after injection
Primary Study Objectives	To assess the diagnostic performance of 18FDCFPyL PET/CT to determine the presence or absence of metastatic disease in patients with high risk PCa prior to prostatectomy (Cohort A)	To determine the CLR of 18F-DCFPyL PET/CT in the detection of recurrent PCa at the patient level	To compare per-patient detection rate of 18FDCFPyL PET/CT versus that of 18F-FCH PET/CT
Number of Patients Screened and Dosed	Consented: 462 Enrolled and Dosed: 385 - Cohort A: 268 - Cohort B: 117	Consented: 217 Enrolled and Dosed: 208	Consented: 217 Randomized: 215 Enrolled: 215 Dosed: 205
Age: Mean (Range) in Years and Sex (M/F)	65.2 (45–86) years 100% Male	67.9 (43–91) years 100% Male	70 (53–88) years 100% Male
Primary Endpoint	Co-Primary endpoints: Specificity and Sensitivity	Correct localisation rate (CLR) at the patient level, defined as the percentage of patients for whom there was a one-to-one correspondence between localization of at least one lesion identified on 18F-DCFPyL PET/CT imaging and the composite truth standard.	Detection rate (DR): number of patients defined as positive at patient level by the independent readers among the total number of patients assessed (for 18F-DCFPyL and 18F-FCH PET/CT)

		CLR=TP/(TP+FP) × 100% for each 18F-DCFPyL PET/CT central reader across all evaluable patients	

Table 15: Bibliographic data reported in literature

Source of data	Details
Performances of 18F-DCFPyL in Localisation of Primary Prostate Cancer and Primary Staging of High-risk PCa	Thirteen studies: 8 prospective and 5 retrospective studies
Performances of 18F-DCFPyL in Re-staging of Recurrent Prostate Cancer	Twenty-one studies: 14 prospective, 6 retrospective and 1 comparative studies
Change in Management motivated by result of imaging with 18F-DCFPyL	Eleven studies: 1 study in initial staging and 10 studies in biochemical recurrence (BCR)
Meta-analyses	Two meta-analyses: Pan et al., 2021 and Sun et al., 2019; both with nine studies and not performed by the applicant

2.6.5.1. Dose response study(ies)

No formal dose-response study has been submitted with this application.

The selection of clinical dose and optimal imaging timepoint have been established considering the following aspects: image quality, current guidelines for PET radiopharmaceuticals and radiation dose optimization.

A high-quality PET image is one in which the proportion of true counts is maximized while minimizing noise. This value is commonly referred to as the Noise Equivalent Count Rate (NECR). This metric is useful to optimize the administered quantity of radiopharmaceutical by modeling of the Poisson distribution at various dosages. NECR has been shown to increase with injected activity at low levels but then plateau or even decrease at high levels. A nearly maximal value of NECR, where the value ceases to significantly increase with the administered dose, has been recommended as suitable criterion for determining the optimal dosage in a PET clinical study (Karakatsanis et al., 2015).

The European Association of Nuclear Medicine (EANM) has published guidelines for 18F-FDG PET in 2015 which recognize a modern understanding of the quadratic relationship between administered dose and NECR (Boellaard et al., 2015). As such, the recommended range of activity for a 70 kg adult is 182-457 MBq corresponding to 2 and 5 minutes per bed position respectively.

A concept applied to radiopharmaceutical dose selection in conjunction with statistical considerations is the ALARA principle (As Low As is Reasonably Achievable), where a reduced radiation dose to the patient and practitioners are preferred whenever possible. In a study of pediatric dose optimization using 18F-FDG PET, the optimal 90% NECR level for a 76 kg adult was characterized at 370 MBq (Accorsi et al., 2010).

Therefore, an optimal radiopharmaceutical dosage should not only allow for adequate statistical quality (>90% NECR) but also recognise that increasing the administered dose beyond this point results in a sharp increase in radiation dose with minimal gain in NECR. However, a simulation of reduced dose PET data and its effect on image quality was recently reported for 18F-FDG PET/CT (Seith et al., 2017). In this study, the authors concluded that administered doses in oncologic whole body examinations are not recommended to be reduced below 3 MBq/kg body weight due to degradation of the image quality.

Although no formal administered dose finding studies of 18F-DCFPyL were performed by investigators at Johns Hopkins University (JHU) as part of the first-in-man study of this novel PSMA tracer, the dose of 333 MBq was deliberately selected to be in line with both the ALARA principle and current 18F-FDG dose recommendations (Szabo et al., 2015). In that study, the optimal time point of imaging was 1-2 hours post injection, and time per bed position by analysis of lesion uptake was described in a series of whole-body PET images. For these reasons, the applicant has carried forward the 333 MBq dosage as the stated optimal administered dose together with a recommended time per bed position of 2-5 minutes (see also section 2.6.2).

2.6.5.2. Main study(ies)

Table 16. Summary of main studies

Study/ID **Truth Standard**	**Patient Population** **No. Enrolled/ Imaged/** **Evaluable for Primary Efficacy**	**Key Efficacy Endpoints**	**Key Efficacy Results**
OSPREY/PyL2301 Pathology truth standard only	**Cohort A**: High risk PCa 268/268/252	-Specificity and Sensitivity for PLN metastasis[1] -PPV and NPV in PLNs -Sensitivity, specificity, PPV and NPV in the prostate gland -Detection rates compared to conventional imaging -Change in intended management	**-PLNs (N stage)[2]**: Specificity: 96-99%, Sensitivity: 31-42%, PPV: 78- 91%, NPV: 81-84% Relative to the diagnostic performance of conventional imaging (posthoc analysis), sensitivity was comparable, NPV was slightly higher, specificity was improved, and PPV of 18F-DCFPyL PET was 3-fold higher with 18F-DCFPyL PET, notably due to lower FP rate **-Prostate Gland**: PPV: 100%; Sensitivity 95-99% -Detected distant metastasis (M1 stage) in 12.3% of patients (2 M1a, 24 M1b, and 7 M1c) as the most advanced stage by any 18F-DCFPyL reader -Change in intended initial therapy planning: 44%
	Cohort B: Recurrent/ metastatic PCa with radiologic evidence of disease 117/117/93	-Sensitivity and PPV overall -Sensitivity and PPV on the region-level by anatomic disease site -Sensitivity and PPV by PSA levels -Detection rates compared to conventional imaging	-Overall[2,3] Sensitivity 93-99%; overall PPV 81-88% -**Pelvic region**: Sensitivity 93-100%; PPV 75-94% -**Extra-pelvic region**: Sensitivity 91-98%; PPV 83-86% -In PSA <2.0 ng/mL (n=32), Sensitivity 89-100%; PPV 62-89% -Staging shifts**:** 18F-DCFPyL PET upstaged 58% (19/33) of patients from M0 to M1, of whom 91% (10/11) of patients who had extrapelvic biopsies were confirmed M1 by pathology; and down staged 22% (18/82) of patients from M1 to M0, of whom 50% (6/12) had M0 confirmed by pathology
CONDOR/PyL3301 A composite SOT of either pathology, correlative imaging, or PSA response	BCR with noninformative baseline imaging; 208/208/208	-CLR[1] on the patient-level; -Detection rates and PPV by anatomic region and baseline PSA; -Change in intended management	-CLR, patient-level: 85-87%. Of all patients imaged, the TP detection rate[4] was 40-43% -Detected occult disease in 59-66% of patients -**Prostatic region**: Detection rate 18-21%; PPV 75-83% -**Pelvic region**: Detection rate 34-38%; PPV 67-73% -**Extra-pelvic region**: Detection rate 26-31%; PPV 67-70%

			-In patients with PSA <2.0 ng/mL (n=139), CLR ranged from 77-78% -Change in intended management: 64%
PYTHON Truth panel on standard of reference (SOR)	First BCR of PCa after initial treatment with curative intent 215/205/197	-Comparison between 18F-DCFPyL -PET/CT and 18F-FCH PET/CT (SOR): -Detection rates compared to (18F)fluorocholine PET/CT[1] -Sensitivity and Specificity -Change in intended management -Concordance with (18F)fluorocholine PET/CT	**-Per-patient detection rate (18F-DCFPyL vs 18F-FCH PET/CTs):** o Worst-case imputation: 58.0% (n=119/205) vs 40.0% (n=82/205) o Observed cases: 58.2% (n=117/201) vs 40.3% (n=81/201) -**Per-patient detection when considering initial treatment with curative intent (18F-DCFPyL vs 18F-FCH PET/CTs):** o 46.9% (n=69/147) vs 29.9% (n=44/147) in patients treated with RP±eLND o 88.9% (n=48/54) vs 68.5% (n=37/54) in patients treated with RT -**When considering the subgroups of PSA level at first injection**, 18F-DCFPyL PET/CT showed a clear trend in higher detection rate when compared to 18F-FCH PET/CT overall, which was even more noticeable from 0.51 ng/mL (n=31) -**Sensitivity (18F-DCFPyL vs 18F-FCH PET/CTs):** 58.3% vs 40.6% -**Concordance rate:** o Prostate bed :87.3% (95% CI 81.9; 91.3) o PLNs: 73.9% (95% CI 67.3; 79.5) o ePLNs: 86.5% (95% CI 81.0; 90.6]) o Bones: 86.9% (95% CI 81.5; 91.0) o Other organs: 92.0% (95% CI 87.3; 95.1) **Impact on patient management (18F-DCFPyL vs 18F-FCH PET/CTs):** 44.1% (n=90/204) vs 28.7% (n=58/202)

BCR=biochemical recurrence; CLR=correct localisation rate (a measure of PPV based on lesion colocalization); eLND=extended lymph node dissection; FP=false positive; NPV=negative predictive value; PET/CT=positron emission tomography/computed tomography; PLN=pelvic lymph node; PPV=positive predictive value; PSA=prostate-specific antigen; RP=radical prostatectomy; RT=radiation therapy; SOR=standard of reference; SOT=standard of truth; TP=true positive.

[1]Primary endpoint for each respective study

[2]No difference with renal impairment (Section 0)

[3]No prostatic region biopsies evaluated in Cohort B

[4]Key efficacy endpoint of interest (FDA Type B Clinical/Non-clinical PreNDA Meeting, 2020)

OSPREY STUDY (Diagnostic performance against a standard of truth)

Methods

This was a phase 2/3, multi-center, multi-reader, open-label, non-randomized study to evaluate the diagnostic performance and safety of 18F-DCFPyL PET/CT to detect prostate cancer in two patients settings:

- **Study Participants**

Men≥18 years of age with histologically confirmed adenocarcinoma of the prostate. All patients provided informed consent before any study procedures were performed.

Cohort A: Patients with high risk (or very high risk) prostate cancer as defined by National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2016 (clinical stage≥T3a, PSA>20 ng/mL, or Gleason score≥8) and are scheduled to undergo radical prostatectomy (RP) with pelvic lymph node dissection (PLND).

Cohort B: Patients with radiologic evidence of local recurrence or new or progressive metastatic disease on anatomical imaging (CT, MRI, or ultrasound), whole-body bone scan (with 99mTc-MDP or sodium fluoride [18F-NaF]) within 4 weeks of Day 1, and are scheduled for percutaneous biopsy of at least 1 amenable lesion. If the patient had received prior treatment with radiation or ablative therapy, the patient had to have evidence of recurrence outside the confines of prior treated site(s).

Exclusion Criteria

-Patients administered any high energy (>300 KeV) gamma-emitting radioisotope within 5 physical half-lives, or any intravenous iodinated contrast medium within 24 hours, or any high-density oral contrast medium (oral water contrast was acceptable) within 5 days prior to study drug injection.

-Patients with any medical condition or other circumstances that, in the opinion of the Investigator, compromised obtaining reliable data, achieving study objectives, or study completion.

-**Cohort A**: Patients with prior androgen-deprivation therapy or any investigational neoadjuvant agent or intervention.

-**Cohort B:**

1. Prior radiation or ablative therapy to intended site of biopsy, if within the prostate bed.

2. Initiation of new systemic therapy for recurrent and/or progressive metastatic disease since radiographic documentation of recurrence/progression.

- **Treatments**

18F-DCFPyL Injection, sterile solution for intravenous (IV) injection, 333 MBq at the time of administration, was administered by IV catheter in an antecubital vein or equivalent venous access. The bolus administration will be followed by a flush of 5-10 mL steril 0.9% sodium chloride injection, to ensure full delivery of the dose. The median decay corrected dose at the time of administration was 340.4 MBq.

At 1 to 2 hours after injection of 18F-DCFPyL, the patient was asked to void, and whole body CT and PET scans were acquired from the mid-thigh through the vertex of the skull.

Any new prostate cancer therapy was strictly prohibited from the time of study drug administration (Day 1) to surgery (Cohort A), or from the time of radiographic documentation of disease progression to biopsy (Cohort B). If a patient received a new prostate cancer therapy (e.g., hormone, drug, biologic, radiologic, chemotherapy) or alternate medical procedure(s) for prostate cancer during these time periods, the patient was withdrawn from the study.

Twelve hours to 28 days post-18F-DCFPyL administration and imaging, patients underwent RP with PLND surgery (Cohort A) or had a follow-up biopsy (Cohort B). Patients whose planned procedure for prostate cancer changed (RP or biopsy) following 18F-DCFPyL PET/CT imaging had any available corresponding histopathology data recorded for the alternate procedure.

Main imaging parameters for PET/CT scanning in the Osprey Study:

PET imaging with 18F-DCFPyL was performed locally using PET/CT scanners with low dose non-enhancing CT for correction of physical effects (e.g., attenuation, scatter) and anatomic localization (transmission scan). Only oral water contrast was acceptable.

Main parameters for PET/CT scanning were consistent through clinical studies.

Mode:3D

Patient Position: Supine with arms above head (unless patient is unable).

Emission Scan: 2-5 min/bed position.

Scan Field of View/Coverage: Mid-thigh through the vertex of the skull and must include bed positions of lower extremities if there is known or suspected disease. Scan from caudal/inferior to superior direction to reduce amount of tracer present in the bladder.

Image Reconstruction: Iterative reconstruction algorithms shall be used (rather than filtered back projection). If available, Time of Flight (TOF) should be used.

Views: non-attenuation corrected, attenuation-corrected and CT for attenuation correction.

- **Objectives**

The primary objective of the study was to assess the diagnostic performance of 18F-DCFPyL PET/CT imaging to determine the presence or absence of metastatic disease in pre-prostatectomy patients with high risk prostate cancer (**Cohort A**).

The secondary objectives were:

• To evaluate the safety and tolerability of 18F-DCFPyL

• To assess the diagnostic performance of 18F-DCFPyL PET/CT imaging to determine the presence or absence of prostate cancer within sites of metastasis or local recurrence (**Cohort B**)

• To determine detection rates of 18F-DCFPyL PET/CT and conventional imaging among lesion locations (e.g., bone, lymph nodes, soft tissue, prostate gland)

• To determine PPV and NPV of 18F-DCFPyL PET/CT imaging

• To determine the pharmacokinetics (PK), biodistribution, and excretion of 18F-DCFPyL

Diagnostic performance characteristics of 18F-DCFPyL PET/CT imaging were evaluated using local histopathology as the truth standard. Three independent readers from a central imaging core lab were given access to 18F-DCFPyL PET/CT imaging, conventional imaging, and imaging at biopsy. The central readers were all blinded to all other clinical information and histopathology assessments. Local pathologists who generated the histopathology results for the primary endpoint remained blinded to imaging results.

The focus was on detection of PLN metastasis with 18F-DCFPyL PET/CT imaging in pre-prostatectomy patients with at least high-risk prostate cancer (Cohort A). Cohort B evaluated detection of disease recurrence and metastases with 18F-DCFPyL PET/CT imaging for comparison with existing radiographic evidence of disease by conventional imaging modalities.

- **Outcomes/endpoints**

Co-Primary Efficacy Endpoints

1. Specificity of 18F-DCFPyL PET/CT imaging to determine the absence of metastatic prostate cancer within the pelvic lymph nodes relative to histopathology in Cohort A.

2. Sensitivity of 18F-DCFPyL PET/CT imaging to determine the presence of metastatic prostate cancer within the pelvic lymph nodes relative to histopathology in Cohort A.

Secondary Efficacy Endpoints

1. Sensitivity of 18F-DCFPyL PET/CT imaging to detect prostate cancer within sites of metastasis or local recurrence relative to histopathology in Cohorts B.

2. Comparison of detection rates[2] for lesion counts overall and by location (i.e., bone, lymph nodes, soft tissue, prostate gland) between 18F-DCFPyL PET/CT and conventional imaging in Cohorts A and B combined.

3. PPV of 18F-DCFPyL PET/CT imaging to predict prostate cancer within the prostate gland and lymph nodes in Cohort A.

4. NPV of 18F-DCFPyL PET/CT imaging to predict the absence of prostate cancer within the prostate gland and lymph nodes in Cohort A.

5. PPV of 18F-DCFPyL PET/CT imaging to predict prostate cancer within sites of local recurrence and other metastatic lesions in Cohort B.

6. Pharmacokinetic parameters derived from blood samples [e.g., Cmax, area under the curve (AUC), total clearance (CL), steady-state volume of distribution (Vss), and mean residence time (MRT)] (subset of Cohorts A and B combined).

- **Sample size**

The planned total sample size for this study was 377 patients, including 262 patients in Cohort A and 115 patients in Cohort B. This study was powered based on the primary analysis in Cohort A, which

[2] Detection Rates (DR) per patient (overall) or per region (location) is when a patient or region is defined as positive by a diagnostic procedure among the total of patients or regions analysed

tested the coprimary endpoints of sensitivity and specificity of 18F-DCFPyL PET imaging relative to histopathology for the Evaluable Set of patients in Cohort A with metastatic disease. For each coprimary endpoint, there were three independent imaging readers. At least two of the three readers had to reject the null hypothesis for specificity to be deemed a success.

If specificity was a success, then the same two readers needed to reject the null hypothesis for sensitivity, leading to overall success of the co-primary endpoints.

A total of 262 patients from Cohort A provided 80% power to reject the null hypothesis about sensitivity at the 5% significance level if the true sensitivity was at least 60% and at least 80% power to reject the null hypothesis about specificity at the 5% significance level if the true specificity was at least 87.8%. These calculations were based on the assumption that the probability of a positive histopathology sample in Cohort A is 20% and a 10% dropout or non evaluable rate in Cohort A. The sample size was based on the normal approximation to the binomial distribution without a continuity correction.

The type I error rate was preserved at 5% by requiring that both null hypotheses be rejected to draw the conclusion that 18F-DCFPyL was efficacious for imaging. The second primary endpoint was to be tested only if the first primary endpoint was rejected at the 0.05 level of significance per a fixed sequential method. If the first hypothesis failed to be rejected, no further testing was to be conducted.

No formal power calculations were performed for Cohort B since it was not a primary endpoint.

No interim analyses were performed.

- **Randomisation**

This was an open-label, non-randomized study involving two cohorts of distinct patient populations. Patients were sequentially assigned to receive 18F-DCFPyL Injection in either Cohort A or Cohort B based on eligibility criteria and with competitive enrollment between study sites.

Blinding (masking)

This was an open-label study, and all patients received 18F-DCFPy.

Three independent readers from a central imaging core laboratory were given access to the 18F-DCFPyL PET/CT images for evaluation according to a one-reader paradigm, without being informed by either of the other two radiologists. One independent central reader was given access and evaluated the conventional imaging scans (including baseline conventional imaging and biopsy-images) for evaluation, without being informed by the 18F-DCFPyL PET/CT results. All central readers were blinded to all other clinical information (including histopathology) and radiology assessments.

Each Investigator was responsible for ensuring that local pathologists who generated the histopathology results for the primary endpoint remained blinded to all imaging results.

- **Statistical methods**

Primary Efficacy: The primary analysis was to test the co-primary endpoints of sensitivity and specificity of 18F-DCFPyL PET imaging for the determination of PLN metastases relative to histopathology for the Evaluable Set in Cohort A. The evaluable subjects in Cohort A were those who

were dosed, had a prostatectomy or lymphadenectomy, and provided a 18F-DCFPyL PET image result (positive or negative) and a corresponding histopathology result (positive or negative).

The null hypotheses was tested in the following order:

1. Specificity of 18F-DCFPyL PET/CT relative to histopathology in Cohort A (H0):

$\pi_{Sp} = 0.80$ versus H1: $\pi_{Sp} \neq 0.80$

2. Sensitivity of 18F-DCFPyL PET/CT relative to histopathology in Cohort A (H01):

$\pi_{Se} = 0.40$ versus H11: $\pi_{Se} \neq 0.40$

where π_{Se} was the true sensitivity and π_{Sp} was the true specificity of 18F-DCFPyL PET imaging.

The point estimates and 95% confidence interval based on the normal approximation to the binomial were presented when the assumptions were met for this. These assumptions stated that the sample size was such that np>5 and n(1-p)>5, where n is the sample size and p is the binomial probability. If this assumption was not met, then an Agresti-Coull confidence interval was presented instead. The null hypothesis for specificity was rejected when the lower limit of the 95% CI exceeded 80% for at least two of the three independent central PET/CT readers. When statistical significance was achieved for specificity where the null hypothesis was rejected, then sensitivity was tested where the null hypothesis would have been rejected when the lower limit of the 95% CI exceeded 40% for the same two readers who rejected the null hypothesis for specificity.

40% sensitivity and 80% specificity for null hypotheses were based on data reported in literature.

The primary analysis in Cohort A tested the co-primary endpoints of sensitivity and specificity of 18F-DCFPyL PET imaging relative to the presence or absence of PLN metastases at surgical pathology. For each co-primary endpoint, there were three independent 18F-DCFPyL imaging readers. At least two of the three readers had to reject the null hypothesis for specificity to be deemed a success. If specificity was a success, then the same two readers needed to reject the null hypothesis for sensitivity leading to overall success of the primary endpoint. The following statistics were computed:

-Sensitivity = true positive (TP)/positive lobe or biopsy (R(p)),

-Specificity = true negative (TN)/negative lobe or biopsy (R(n)),

-PPV = TP/positive lesion (I(p))

-NPV = TN/negative lesion (I(n))

For Cohort A, a true positive or true negative value was determined based on imaging and histopathology aligning on outcome. The estimation of sensitivity and specificity was based upon findings from the independent readers at the central imaging core laboratory.

The primary analysis for patients in Cohort A was addressed by computing point estimates and 2-sided 95% CIs for specificity first. When the lower limit of the 95% CI exceeded 80% for at least two of the three readers and the null hypothesis was rejected for specificity, then sensitivity was tested next. Specificity and sensitivity were computed for each of the three independent central readers. A sensitivity analysis of the co-primary endpoint was performed to allow any two of the three central PET/CT readers to reject the null hypothesis for sensitivity only after specificity had been deemed a success. Additional sensitivity analyses of the co-primary endpoint were performed post-hoc.

Analysis of Secondary and Exploratory Efficacy Endpoints

Analysis of secondary efficacy endpoints was conducted regardless of the outcomes of the primary analyses. Diagnostic testing and imaging detection rates were analyzed for the Evaluable Set. Point

estimates and 2-sided 95% CIs for PPV and NPV were computed for the prostate gland in Cohort A for the Evaluable Set. The normal approximation to the binomial distribution was planned when the assumption was met. Otherwise, the Agresti-Coull confidence interval was presented instead. PPV and NPV were computed for each of the three independent PET/CT readers at the central imaging core laboratory.

Point estimates and 2-sided 95% CIs for PPV and sensitivity were computed from the conventional guided biopsy obtained from patients in Cohort B for the Evaluable Set. The normal approximation to the binomial distribution was planned where assumptions were met. In cases when assumptions were not met, CIs would be derived from the Agresti-Coull method. Results were computed for each of the 3 independent readers from the central imaging core lab. The null hypothesis would be rejected if the lower limit of the 95% CI exceeded 0.5 for each of the three central readers.

Safety analyses: Duration of safety follow-up was 7 (±3) days after 18F-DCFPyL dosing if surgery (Cohort A) or biopsy (Cohort B) had not occurred; and 21 (±7) days post biopsy (Cohort B).

Definition of populations for analysis

Safety Set: includes all patients who received any amount of 18F-DCFPyL.

Evaluable Set: The Evaluable Set in Cohort A includes those patients who received 18F-DCFPyL, had a prostatectomy or lymphadenectomy, and provided a 18F-DCFPyL PET image result (positive or negative) and a corresponding histopathology result (positive or negative).

The Evaluable Set in Cohort B includes those patients who received 18F-DCFPyL, underwent a conventional image-guided biopsy, and provided an 18F-DCFPyL PET image result (positive or negative) and a corresponding histopathology result (positive for prostate cancer or negative), along with a conventional image that confirmed the location of the histopathology sample.

Change in Planned Protocol Procedure set includes dosed patients in Cohort A who did not have a prostatectomy and lymphadenectomy due to change of planned management, and patients in Cohort B who did not have conventional image-guided biopsy due to change of planned management.

Per Protocol set includes those patients in the Evaluable Set without any major protocol deviations. Major protocol deviations were identified prior to database lock and analysis.

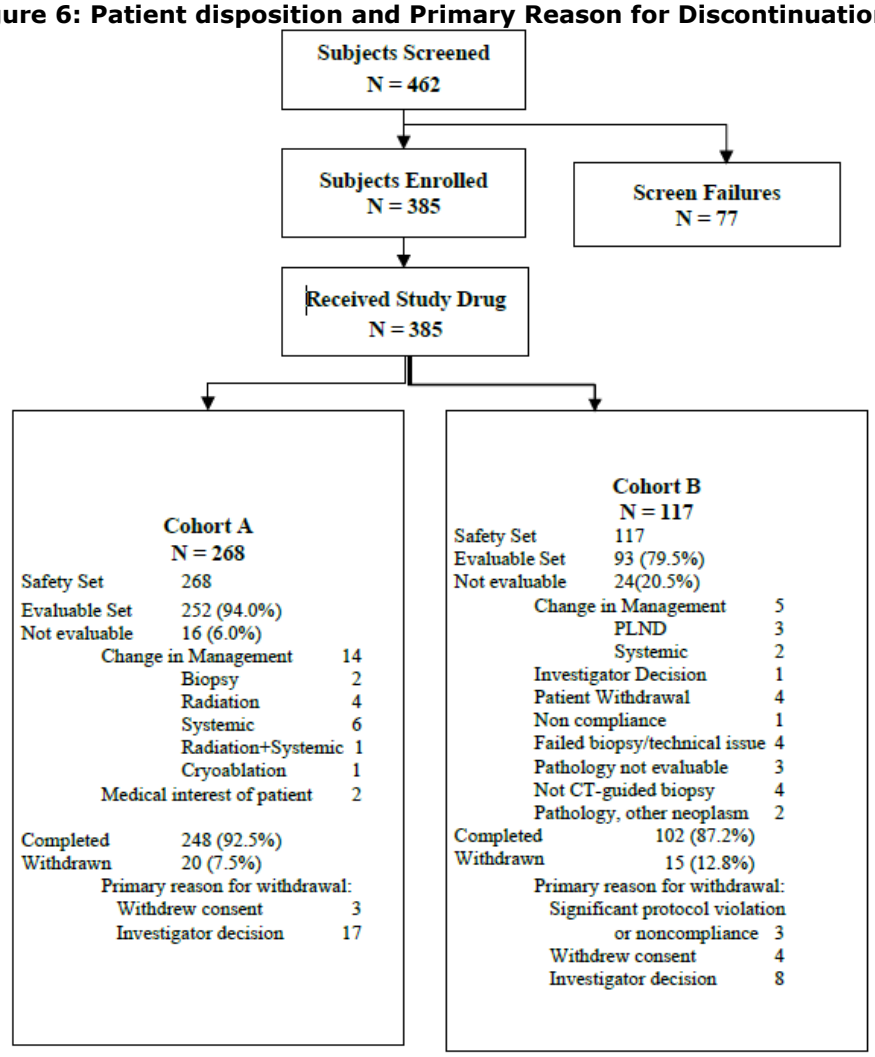
PK Blood Set includes those patients who provided at least six of the nine scheduled blood samples.

PK Urine Set includes those patients with at least two of the three scheduled urine collections.

Results

- **Participant flow**

Figure 6: Patient disposition and Primary Reason for Discontinuation from the Study



OSPREY cohort A enrolled a cohort of 268 men with high-risk biopsy-proven prostate cancer who were considered candidates for radical prostatectomy and pelvic lymph node dissection. Each patient received a single piflufolastat (18F) PET/CT from mid-thigh to skull vertex. Three central independent readers blinded to all clinical information interpreted each PET scan for the presence of abnormal uptake in pelvic lymph nodes in multiple subregions, including the common iliac lymph nodes.

A total of 252 patients (94%; cohort A evaluable set) underwent prostatectomy and pelvic lymph node dissection and had sufficient histopathology data for evaluation of the pelvic lymph nodes. Surgical specimens were separated into three regions: left hemipelvis, right hemipelvis, and other. For each patient, piflufolastat (18F) PET/CT results and histopathology results obtained from dissected pelvic lymph nodes were compared by surgical region. PET/CT results in locations that were not dissected were excluded from analysis.

- **Recruitment**

The study period was approximately 20 months from the time the first patient was enrolled, 30 November 2016, to the time the last patient underwent follow-up procedures, 19 July 2018. A total of

462 patients were screened for participation in this study. Of these, 77 (16.7%) patients were screen failures. A total of 385 (83.3%) patients were enrolled and received study drug across 10 sites in the US (n=8) and Canada (n=2). At the end of the study, 350 (90.9%) patients had completed participation and 35 (9.1%) patients had withdrawn. The reasons for withdrawal from the study were Investigator decision (6.5%, n=25), withdrawal of consent (1.8%, n=7), or significant protocol violation or noncompliance (2.6%, n=3).

- **Conduct of the study**

The original protocol was approved on 12 July 2016. There were two protocol amendments that were submitted to the appropriate Institutional Review Boards (IRBs) for information and approval in accordance with local requirements, and approval was obtained before any changes were implemented. No patient was enrolled prior to the implementation of Protocol Amendment 01.

- **Baseline data**

-Demographics and PCa disease characteristics in Cohort A (safety set)

Patients had a median age of 65 (range: 46 to 84) years. Patient characteristics of high-risk PCa included a total Gleason score ≥8 in 81% of patients, clinical T stage ≥T3a in 27% of patients and PSA >20 ng/mL in 18% of patients. The median PSA was 9.7 ng/mL (range 1.2-125.3 ng/mL). Almost all patients had no known disease in the regional lymph nodes (NX/N0, 97%) or distant metastasis (MX/M0, 99%) based on last AJCC staging (median 1.7 months prior to study entry). All patients were pre-prostatectomy, reflective of the target population.

All Cohort A patients underwent baseline imaging with CT/MRI and whole-body bone scan. Based on central imaging evaluation by an independent, blinded central imaging reviewer, 61% of patients were N0 (n=164) and 82% of patients were M0. There were notably more suspicious metastatic findings by the central review than clinical staging by AJCC, owing to the known diagnostic performance limitations with CT/MRI. CT/MRI alone may misrepresent the extent of disease and is not reliable to determine pelvic nodal metastasis (~40% sensitivity coupled with low PPV [32% for CT and 47% for MRI]) (Hövels et al., 2008).

For the 252 evaluable patients, the mean age was 64 years (range 46 to 84 years). The median serum PSA was 9.3 ng/mL. The total Gleason score was 7 for 19%, 8 for 46%, and 9 for 34% of the patients, with the remainder of the patients having Gleason scores of 6 or 10.

-Demographics and PCa disease characteristics in Cohort B (safety set)

Patients had a median age of 68 (range 45 to 86) years. PCa history and baseline disease characteristics demonstrate that Cohort B patients span the spectrum of recurrent disease, ranging from patients who were hormone naïve (38% with no prior ADT use) with low PSA levels (27% with PSA <2.0 ng/mL), to patients with M1 (37%) by AJCC staging. Notably, baseline conventional imaging staged 28% (n=33) of patients with M0 (no extra-pelvic metastases) radiographic disease state and 70% (n=82) with a distant metastatic lesion (M1) at study entry.

-Baseline Conventional Imaging (safety sets):

All patients (safety set) had a baseline CT or MRI scan and a whole body bone scan as required per protocol. The majority (97.1%) of patients had contrast-enhanced CT and 99mTc-MDP bone scan (82.3%) at baseline.

Prior Prostate Cancer Treatments

In Cohort A (safety set), no patients had prior prostatectomy. 264 (98.5%) of patients received no prior anticancer therapy.

For Cohort B (safety set), as expected with the target population, the majority (63.2%) of patients received prior systemic prostate cancer therapy, with a median of 4 treatment regimens received (range 1 to 11). Forty-three (36.8%) patients did not receive any prior systemic prostate cancer therapy. A total of 47.0% received prior prostatectomy and 58.1% underwent prior prostate RT.

- **Numbers analysed**

The number of patients included in each analysis set is reflected below:

A total of 462 patients provided informed consent; 77 were screen failures and 385 patients were enrolled (268 in Cohort A and 117 in Cohort B) and received 18F-DCFPyL and underwent PET/CT imaging.

Table 17. Analysis Sets

Parameter	Cohort A (N=268) n (%)	Cohort B (N=117) n (%)	Total (N=385) n (%)
Safety Set[1]	268 (100)	117 (100)	385 (100)
Evaluable Set[2]	252 (94.0)	93 (79.5)	345 (89.6)
Per Protocol Set[3]	246 (91.8)	92 (78.6)	338 (87.8)
Change in Planned Protocol Procedure Set[4]	14 (5.2)	5 (4.3)	19 (4.9)
PK Blood Set[5]	10 (3.7)	0	10 (2.6)
PK Urine Set[6]	10 (3.7)	0	10 (2.6)

[1]The Safety Set includes all patients who received any amount of 18F-DCFPyL.
[2]The Evaluable Set consists of patients who received study drug, underwent prostatectomy and lymphadenectomy (Cohort A) or conventional image-guided biopsy (Cohort B), and had results for an 18F-DCFPyL PET/CT scan and corresponding histology.
[3]The Per Protocol set consists of the Evaluable Set excluding any patient with a major protocol violation.
[4]The Change in Planned Protocol Procedure set includes patients who received 18F-DCFPyL but did not undergo prostatectomy and lymphadenectomy (Cohort A) or image-guided biopsy (Cohort B).
[5]The PK Blood Set includes patients who had at least six of the nine scheduled blood samples.
[6]The PK Urine Set includes patients who had at least two of the three scheduled urine samples.

- **Outcomes and estimation**

Osprey Study Cohort A

Co-Primary Efficacy Results (Diagnostic performance for pelvic nodal metastases)

Results for specificity reached significance, as the lower limit of the 95% CI of all 3 readers exceeded the success criteria of 80% confidence limit. Of the 190 (75.4%) men with no pathologic PLN lesion(s), specificity across all 3 independent 18F-DCFPyL PET/CT readers was very high, ranging from 96.3% to 98.9% (lower limit of the 95% CI: 93.6%-96.0%).

Results for sensitivity did not reach significance, as the lower bound of the 95% CI (19.2% to 29.7%) for at least 2 of the 3 readers did not exceed the required success criteria of 40% confidence limit. Sixty-two (24.6%) men had at least one pathologic PLN lesion for prostate cancer metastases. Sensitivity across all three independent 18F-DCFPyL PET/CT readers ranged from 30.6% to 41.9% (lower bound of 95% CI: 19.2%-29.7%). A summary of results is shown in the next table:

Table 18: Diagnostic Performance of 18F-DCFPyL PET/CT for Determining PLN Metastasis, OSPREY Cohort A (Evaluable Set)

Parameter	Reader 1 N=252 % (95% CI)[1]	Reader 2 N=252 % (95% CI)[1]	Reader 3 N=252 % (95% CI)[1]
Negative Histology	190	190	190
FP	4	2	7
TN	186	188	183
Specificity	97.9 (94.5, 99.4)[2]	98.9 (96.0. 100)[2]	96.3 (93.6, 99.0)
Positive Histology	62	62	62
FN	36	43	37
TP	26	19	25
Sensitivity	41.9 (29.7, 54.2)	30.6 (19.2, 42.1)	40.3 (28.1, 52.5)
Negative Imaging	222	231	220
FN	36	43	37
TN	186	188	183
NPV	83.8 (78.9, 88.6)	81.4 (76.4, 86.4)	83.2 (78.2, 88.1)
Positive Imaging	30	21	32
FP	4	2	7
TP	26	19	25
PPV	86.7 (69.7, 95.3)[2]	90.5 (69.9, 98.6)[2]	78.1 (63.8, 92.5)

CI=confidence interval; FN=false negative; FP=false positive; NPV=negative predictive value; PLN=pelvic lymph node; PPV=positive predictive value; TN=true negative; TP=true positive.

[1]95% CI=two-sided CI derived from a 1-sample binomial, where the null hypothesis was 0.8 for specificity and 0.4 for sensitivity.

[2]95% CI=2-sided 95% CI derived from the Agresti-Coull method.

Primary Analysis: The same two readers had to reject the null hypothesis for specificity and sensitivity for this analysis of co-primary endpoints to be deemed a success.

Sensitivity Analysis: Any two readers had to reject the null hypothesis for specificity and sensitivity for this analysis of co-primary endpoints to be deemed a success.

Table 22 below shows piflufolastat (18F) PET/CT performance by reader using pelvic lymph node histopathology as standard of truth, at the patient-level with region matching (one true positive region defines a true positive patient). Approximately 24% of the evaluable patients had pelvic lymph node metastases based on histopathology (95% confidence interval: 19%, 29%).

Table 19. Performance evaluation of piflufolastat (^{18}F) PET/CT for pelvic lymph node metastasis detection in OSPREY cohort A (n=252) using Patient-Level and Region-Matched analysis.

	Reader 1	Reader 2	Reader 3
True positive	23	17	23
False Positive	7	4	9
False Negative	36	43	37
True Negative	186	188	183
Sensitivity, % (95% CI)	39 (27;51)	28 (17;40)	38 (26;51)
Specificity, % (95% CI)	96 (94;99)	98 (95;99)	95 (92;98)
PPV, % (95% CI)	77 (62;92)	81 (59;93)	72 (56;87)
NPV, % (95% CI)	84 (79;89)	81 (76;86)	83 (78;88)

Abbreviations: CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value

Osprey Study Cohorts A and B (Inter- and intra-reader variability)

Inter- and intra-reader variability were assessed for the central imaging readers. When evaluating PLN lesions from the Cohort A Safety Set, Fleiss' generalised kappa statistic showed a high level of agreement between readers at 0.78 with a 95% confidence interval (CI) of (0.71, 0.85).

When the PLN reads were examined for Cohorts A and B combined, the kappa increased to 0.83. The inter-reader variability for the central readers by all biopsy images for Cohort B showed moderate agreement of 84.2%, with kappa statistic at 0.58 (95% CI 0.47, 0.70). Intra-reader variability for Cohort B images was not assessed. Intra-reader (test-retest) variability was assessed on a subset of images. For Cohort A (Safety Set), Cohen's kappa was high at 0.70 for Reader 2 and showed perfect agreement (kappa=1.00) for Readers 1 and 3 for 19-21 images that were re-read when determining PLN metastasis. When combing the PLN re-reads for Cohorts A and B combined, Cohen's kappa ranged from 0.79 to 1.00, which is a high to excellent rate of agreement in 29 images.

Osprey Study Cohort A (Change in intended management)

Changes to the clinical management plans were evaluated based on a prospective review of individual patient-level baseline clinical and conventional imaging data before and after 18F-DCFPyL PET by an independent central panel of disease experts using Medical Management Questionnaires completed before and after seeing 18F-DCFPyL PET/CT results. This review was performed on all Cohort A patients who underwent 18F-DCFPyL PET/CT imaging (Cohort A Safety Set).

Overall, the data showed that 18F-DCFPyL PET/CT led to a change in management in 43.6% (115/264) of patients with high risk prostate cancer based on both positive and negative 18F-DCFPyL PET/CT scans.

Sensitivity and PPV of 18F-DCFPyL PET/CT to Detect Prostate Cancer within Sites of Locoregional Recurrence or Metastasis (Cohort B)

Sensitivity and PPV were 92.9-98.6% (95% CI, 84.0-100) and 81.2-87.8 (95% CI, 72.9-95.3) for the three readers respectively when all lesions were considered. There were also acceptable values of sensitivity and PPV by anatomic region (data not shown).

- **Ancillary analyses**

Ancillary analyses in Osprey Study Cohort A

Post-hoc Sensitivity Analysis Excluding Pathologic Lesions ≤5 mm in Metastatic Foci Size

A post-hoc sensitivity analysis of the co-primary endpoint was performed in cohort A (Osprey study) excluding patients (n=27) who had pathologic PLN(s) with metastatic lesion size(s) below the PET detection limitation (≤5 mm) to account for the intrinsic detection limits of PET scanners for small lymph node metastases.

The results of this analysis are shown in the following table. In this subset excluding men whose metastatic PLN lesions were below the PET scanner resolution (≤5 mm), 18FDCFPyL PET/CT demonstrated equally high specificity as in the primary analysis on the full Evaluable Set. Further, sensitivity met the success criteria whereby the lower limit of the 95% CI exceeded 40% for the same two readers that rejected the null hypothesis for specificity. Additionally, 18F-DCFPyL PET/CT demonstrated equally high PPV and NPV as in the primary analysis on the full Evaluable Set.

Table 20: Diagnostic Performance of 18F-DCFPyL PET/CT in the Pelvic Lymph Nodes Excluding Patients with Maximum Pathologic Lymph Node Size ≤ 5mm, Cohort A, Evaluable Set

		Reader 1		Reader 2		Reader 3	
Parameter	**Statistic**	N=255	95% CI (%)	N=255	95% CI (%)	N=255	95% CI (%)
Negative Histology	N	190		190		190	
False Positive	N	4		2		7	
Specificity	n (%)	186 (97.9)	(94.52, 99.37)[1]	188 (98.9)	(96.00, 99.96)[1]	183 (96.3)	(93.64, 98.99)
Positive Histology	N	35		35		35	
False Negative	N	13		18		14	
Sensitivity	n (%)	22 (62.9)	(46.85, 78.86)	17 (48.6)	(32.01, 65.13)	21 (60.0)	(43.77, 76.23)
Negative Imaging	N	199		206		197	
False Negative	N	13		18		14	
NPV	n (%)	186 (93.5)	(90.03, 96.90)	188 (91.3)	(87.41, 95.12)	183 (92.9)	(89.31, 96.48)
Positive Imaging	n	26		19		28	
False Positive	n	4		2		7	
PPV	n (%)	22 (84.6)	(65.85, 94.47)[1]	17 (89.5)	(67.37, 98.30)[1]	21 (75.0)	(58.96, 91.04)

CI=confidence interval; NPV=negative predictive value; PPV=positive predictive value. The Evaluable Set consisted of dosed patients in Cohort A who received a prostatectomy or lymphadenectomy and had an 18F-DCFPyL PET imaging result and a corresponding histology result. 95% CI= 2-sided 95% CIs were derived from normal approximation to 1-sample binomial distribution. [1]95% CI = 2-sided 95% CI derived from the Agresti-Coull method.

Post-hoc Colocalization Analysis (Pelvic Lymph Node Colocalisation Analysis in cohort A)

The co-primary endpoint was analyzed for colocalisation as a post-hoc sensitivity analysis based on TP results, defined as 18F-DCFPyL PET/CT imaging and histopathology positive in the same anatomic location, defined as the right template, left template, pre-sacral lymph nodes, or other lymph nodes. Results are shown in the following table.

Table 21: Diagnostic Performance of 18F-DCFPyL PET/CT – PLNs Colocalisation Analysis, Cohort A (Evaluable Set)

	Reader 1 N=252 n (%) (95% CI)[1]	**Reader 2 N=252 n (%) (95% CI)[1]**	**Reader 3 N=252 n (%) (95% CI)[1]**
Negative Histology	190	190	190
FP	4	2	7
TN	186	188	183
Specificity	97.9 (94.5, 99.4)[2]	98.9 (96.0, 100)[2]	96.3 (93.6, 99.0)
Positive Histology	62	62	62
FN	39	45	39
TP	23	17	23
Sensitivity	37.1 (25.1, 49.1)	27.4 (16.3, 38.5)	37.1 (25.1, 49.1)
Negative Imaging	225	233	222
FN	39	45	39
TN	186	188	183
NPV	82.7 (77.7, 87.6)	80.7 (75.6, 85.8)	82.4 (77.4, 87.4)
Positive Imaging	27	19	30
FP	4	2	7
TP	23	17	23
PPV	85.2 (66.9, 94.7)[2]	89.5 (67.4, 98.3)[2]	76.7 (61.5, 91.8)

CI=confidence interval; FN=false negative; FP=false positive; NPV=negative predictive value; PET/CT=positron emission tomography/computed tomography; PPV=positive predictive value.

The Evaluable Set consisted of dosed patients in Cohort A who received a prostatectomy or lymphadenectomy and had an 18F-DCFPyL PET imaging result and a corresponding histology result.

[1]Two-sided CI derived from a 1-sample binomial, where the null hypothesis was 0.8 for specificity and 0.4 for sensitivity.

[2]Two-sided 95% CI derived from the Agresti-Coull method.

Specificity was unchanged for all three readers from the primary efficacy results. Sensitivity across all three readers ranged from 27% to 37%, slightly lower than the primary efficacy results of 31% to 42%. Notably, PPV and NPV remained unchanged relative to the pre-specified secondary endpoints, with PPV across all three readers ranging from 77% to 90% and NPV ranging from 81% to 83%.

Post-hoc Comparison of Diagnostic Performance with Baseline Conventional Imaging in Patients with High Risk Prostate Cancer (Cohort A)

When compared to centrally read conventional imaging (CT or MRI) for determining pelvic lymph node metastases in a post-hoc analysis, 18F-DCFPyL PET/CT demonstrated a 3-fold higher PPV than conventional imaging (median 86.7% vs. 28.3%, respectively) despite similar sensitivity (median 40.3% for 18F-DCFPyL PET/CT and 42.6% for conventional imaging). 18F-DCFPyL PET/CT was also more specific than conventional imaging (median 97.9% vs. 65.1%, respectively and had a slightly higher NPV than conventional imaging (median 83.2% vs. 78.8%, respectively).

Exploratory analyses on the diagnostic performance of piflufolastat (18F) in OSPREY cohort A for detection of pelvic lymph node metastases, with region matching, stratified by tumor stage

In exploratory analyses, there were numerical trends towards more true positive results among patients with total Gleason score of 8 or higher and among patients with tumor stage of T2c or higher relative to those patients with lower Gleason score or tumor stage (FDA, CDER Multi-discipline review, clinical review, Pylarify (piflufolastat (18F)), 2021).

Table 22. Patient-level performance of piflufolastat (^{18}F) for detection of pelvic lymph node metastases, with region matching, stratified by total Gleason score

Diagnostic performance measure	Reader 1		Reader 2		Reader 3	
	Gleason ≤ 7 (n=49)	Gleason ≥ 8 (n=203)	Gleason ≤ 7 (n=49)	Gleason ≥ 8 (n=203)	Gleason ≤ 7 (n=49)	Gleason ≥ 8 (n=203)
True Positive	2	21	1	16	2	21
False positive	0	7	0	4	1	8
False negative	8	28	9	34	8	29
True negative	39	147	39	149	38	145
Sensitivity point estimate (95%CI)	0.20 (0.05-0.52)	0.43 (0.29-0.57)	0.10 (0-0.43)	0.32 (0.19-0.45)	0.20 (0.05-0.52)	0.42 (0.28-0.56)
Specificity point estimate (95% CI)	1 (0.89-1)	0.95 (0.92-0.99)	1 (0.89-1)	0.97 (0.93-0.99)	0.97 (0.86-1)	0.95 (0.91-0.98)

PPV point estimate (95%CI)	1 (0.29-1)	0.75 (0.59-0.91)	1 (0.17-1)	0.80 (0.58-0.93)	0.67 (0.20-0.94)	0.72 (0.56-0.89)
NPV point estimate (95%CI)	0.83 (0.72-0.94)	0.84 (0.79-0.89)	0.81 (0.70-0.92)	0.81 (0.76-0.87)	0.83 (0.72-0.94)	0.83 (0.78-0.89)
% pathology positive point estimate (95%CI)	0.20 (0.09-0.32)	0.24 (0.18-0.30)	0.20 (0.09-0.32)	0.25 (0.19-0.31)	0.20 (0.09-0.32)	0.25 (0.19-0.31)

Ancillary analyses in Osprey Study Cohort B

Post-hoc Analysis of Sensitivity and PPV by Baseline PSA (Cohort B)

Sensitivity and PPV values were high across all PSA ranges in men with suspected recurrent or metastatic prostate cancer. In men with low PSA values (<2 ng/mL), sensitivity ranged 88.9%-100% and PPV ranged from 62-89%.

Staging Shifts from Baseline Conventional Imaging to 18F-DCFPyL PET Imaging

In OSPREY Cohort B, 82 (70%) patients had baseline radiographic M1 stage disease (14 patients with M1a, 50 patients with M1b, 18 patients with M1c) by central conventional imaging review and 33 (28%) patients were M0 stage at baseline by central conventional imaging review.

18F-DCFPyL PET upstaged 58% (19/33) of patients from M0 to M1, of whom 91% (10/11) who underwent an extra-pelvic biopsy were confirmed to have M1 disease by pathology, including 9 patients with M1b and 1 patient with M1a.

Within M1 stage, 18F-DCFPyL PET upstaged 16% (10/64) of patients to a higher M1 sub-stage.

Only one patient underwent biopsy of the upstaged lesion, which was confirmed positive by pathology (M1b).

Of the patients who were staged M1 at baseline, 18F-DCFPyL PET/CT down staged 22% (18/82) to M0, and 50% (6/12) who underwent an extrapelvic biopsy were confirmed to have no distant metastasis by pathology (M0).

CONDOR STUDY (Diagnostic performance and Clinical Impact in BCR patients with non-informative baseline imaging)

Methods

This is a phase 3, multi-center, open-label, single-arm, non-randomized study to evaluate the diagnostic performance and safety of 18F-DCFPyL PET/CT in patients with suspected recurrence of prostate cancer and negative or equivocal findings per institutional standard of care conventional imaging.

Study participants

Men≥18 years of age with histologically confirmed prostate adenocarcinoma per original diagnosis, with subsequent definitive therapy. All patients provided informed consent before any study procedures were performed.

Eligible patients were enrolled in a non-randomized, sequential manner. Patient enrollment and follow-up assessments concluded when the study reached the required number of patients evaluable for calculation of the primary endpoint.

Patients who began any systemic therapy for prostate cancer prior to efficacy follow-up were discontinued from the study.

Inclusion Criteria

1. Men ≥18 years of age.

2. Histopathologically confirmed prostate adenocarcinoma per original diagnosis, with subsequent definitive therapy.

3. Suspected recurrent and/or metastatic prostate cancer based on rising PSA after definitive therapy on the basis of:

    a. Post-RP: Detectable or rising PSA that was ≥0.2 ng/mL with a confirmatory PSA ≥0.2 ng/mL, American Urological Association (AUA) recommendation (Cookson et al. 2007); or

    b. Post-RT, cryotherapy, or brachytherapy: Increase in PSA level that was elevated by ≥2 ng/mL above the nadir, American Society for Therapeutic Radiology and Oncology (ASTRO)-Phoenix consensus definition) (Roach et al., 2006).

4. Negative or equivocal findings for prostate cancer on conventional imaging performed as part of standard of care workup within 60 days prior to Day 1.

5. Life expectancy ≥6 months as determined by the Investigator.

6. Able and willing to provide informed consent and comply with protocol requirements.

Exclusion Criteria

Patients meeting any of the following exclusion criteria were not eligible for this study.

1. Administered any high energy (>300 KeV) gamma-emitting radioisotope within 5 physical half-lives prior to Day 1.

2. Ongoing treatment with any systemic therapy (e.g., ADT, antiandrogen, gonadotropin releasing hormone, GnRH, luteinizing hormone releasing hormone, LHRH, agonist or antagonist) for prostate cancer.

3. Treatment with ADT in the 3 months prior to Day 1.

4. Receipt of investigational therapy for prostate cancer within 60 days prior to Day 1.

5. Any medical condition or other circumstances that, in the opinion of the Investigator, compromises the safety or compliance of the patient to produce reliable data or to complete the study.

Treatments

18F-DCFPyL activity dose, method of administration and timing of scan are the same as the Osprey study.

Enrolled patients received a single dose of 333 MBq 18F-DCFPyL injection followed by a single PET/CT scan acquired at 1-2 hours post-dosing. The median decay corrected dose at the time of administration was 340.4 MBq. Only patients with positive 18F-DCFPyL PET/CT scans (detection of disease at any site) by local assessment were followed at the Efficacy visit(s). Patients underwent Efficacy follow-up based on their 18F-DCFPyL PET/CT finding(s) per local interpretation and clinical presentation for evaluation of the composite truth standard, defined as evaluable local histopathology result for prostate cancer from surgery or biopsy performed within 60 days following 18F-DCFPyL PET/CT; or if evaluable histopathology was unavailable, informative conventional imaging finding(s) of the anatomical correlate to the 18F-DCFPyL-suspected lesion(s) within 60 days following 18F-DCFPyL PET/CT, before other treatment; or if neither histopathology nor conventional imaging was available or informative, confirmed PSA response post-radiation therapy [RT] (no concomitant androgen deprivation therapy [ADT]) that was initiated within 60 days following 18F-DCFPyL PET/CT.

Adverse events (AEs) were assessed following 18F-DCFPyL dosing (Day 1), and again via a safety phone call 7 (±3) days post-18F-DCFPyL dosing.

Each 18F-DCFPyL PET/CT scan was assessed by 3 blinded radiologists who worked independently and did not receive any clinical information or other images for each patient. Each image obtained as part of the composite standard of truth was assessed by the (Imaging) Truth Panel, a distinct panel of 2 independent readers who worked collaboratively. The Truth Panel provided consensus reads of the presence and location(s) of lesions consistent with prostate cancer on conventional imaging, and of the accuracy of targeting of 18F-DCFPyL lesions in imaging obtained during image-guided biopsy.

Medical Management Questionnaires (MMQs) were to be completed by the treating investigator at two time-points during the study to capture planned changes in the clinical management for all subjects who underwent 18F-DCFPyL PET/CT imaging:

- **Prior to 18F-DCFPyL dosing,** the treating investigator will complete the Pre-PyL MMQ based on baseline clinical information and results from conventional imaging.

- **Post-18F-DCFPyL imaging**, the treating investigator will complete the Post-PyL MMQ based on the additional result from local interpretation of the 18F-DCFPyL PET/CT scan, to assess whether a planned change to the initial medical management plan is warranted due to the 18F-DCFPyL finding.

All concomitant medications and medical procedures were recorded in the eCRF from post 18F-DCFPyL dosing (Day 1) and at all subsequent study visits.

Objectives

The primary objective of this study was to determine the Correct Localization Rate (CLR) of 18F-DCFPyL positron emission tomography/computed tomography (PET/CT) imaging in the detection of recurrent prostate cancer at the patient level.

Secondary objectives:

1. To assess the impact of 18F-DCFPyL PET/CT disease detection on patient’s clinical management plans.

2. To evaluate the safety and tolerability of 18F-DCFPyL.

Exploratory objectives:

1. To determine detection rates of disease sites with 18F-DCFPyL PET/CT by region (prostatic, pelvic, extra-pelvic) and baseline prostate specific antigen (PSA).

2. To determine the Positive Predictive Value (PPV) of 18F-DCFPyL PET/CT imaging in the detection of recurrent disease in the prostatic, pelvic, and extra-pelvic regions.

Outcomes/endpoints

Primary Efficacy Endpoints

The CLR at the patient level, defined as the percentage of patients for whom there was a one-to-one correspondence between localization of at least one lesion identified on 18F-DCFPyL PET/CT imaging and the composite truth standard.

Secondary efficacy endpoints

The percentage of patients with a change in intended prostate cancer treatment plans due to 18FDCFPyL PET/CT as measured by comparison of intended management questionnaires completed pre- and post-18F-DCFPyL PET/CT imaging results.

Safety endpoints

-Incidence of treatment-emergent adverse events from time of 18F-DCFPyL dosing up to 7 (±3) days following 18F-DCFPyL dosing.

-Change from baseline to post-18F-DCFPyL injection vital signs.

-Concomitant medications and medical procedures.

Exploratory endpoints

-The detection rates of 18F-DCFPyL PET/CT among lesion locations i.e., prostatic, pelvic, extrapelvic.

-The PPV of 18F-DCFPyL PET/CT for prostatic, pelvic, extra-pelvic regions from the composite truth standard in patients with positive lesion(s) on 18F-DCFPyL PET/CT imaging.

The percentage of patients with positive 18F-DCFPyL PET/CT scans who had negative findings for prostate cancer based on the composite truth standard.

-The detection rates of 18F-DCFPyL PET/CT imaging as a function of baseline PSA groups.

Sample size

The sample size was calculated based on the primary endpoint, the CLR. The assumed CLR of 18F-DCFPyL PET/CT imaging is 30%. Based on the varied published experience with 68Ga-PSMA PET/CT and a meta-analysis (Perera et al., 2016), approximately 76% (95% confidence interval, CI: 66-85%) of PSMA scans are positive in patients with suspected recurrence of prostate cancer following initial therapy, conservatively 60% of subjets, and approximately 30% may be verified by the composite SoT (histopathology or conventional imaging or PSA follow-up post-RT). Then, the use of 18F-DCFPyL PET/CT will permit the detection/localization of recurrent prostate cancer in approximately 18% of the underlying target population, versus at most 5% that could be identified by conventional imaging alone.

The sample size estimates are based on the positive likelihood ratio (PLR) of CLR to prevalence.

The PLR is estimated as PLR=(CLR/1-CLR)/(prevalence/1-prevalence).

Conservatively assuming the initial prevalence rate as a population parameter to be 5% by conventional imaging if a CLR of 30% is realized, the positive likelihood ratio is expected to be 8.1, implying a considerable increase in the clinical value of 18F-DCFPyL PET/CT to identify prostate cancer.

Using a lower bound for the 95% CI for CLR of 20%, the corresponding lower bound for CLR would be 4.75 based on a normal approximation to the Binomial. This will thus require a total of 81 positive 18F-DCFPyL scans, which translates to a total of 134 18F-DCFPyL PET/CT scans or evaluable subjects needed. Accounting for a 30% non-evaluable (including loss to follow-up) rate, approximately 192 subjects will need to undergo 18F-DCFPyL PET/CT in the study.

Randomisation

This was an open-label, non-randomized study.

Blinding (masking)

This was a single-arm, open-label study. All enrolled patients received 18F-DCFPyL.

For local interpretation of 18F-DCFPyL PET/CT imaging, local readers were not blinded to clinical or other locally generated imaging results. If tissue was obtained, each Investigator was responsible for ensuring that local pathologists remained blinded to all locally generated imaging results.

For primary endpoint analysis of 18F-DCFPyL PET/CT imaging evaluation by central readers, there was a central imaging core laboratory to provide blinded, independent imaging review services. This review was comprised of two discrete imaging evaluations:

1. 18F-DCFPyL PET/CT assessment comprised of three blinded nuclear medicine readers (i.e., radiologists). The readers were blinded to all clinical information, including any other imaging available for a given patient. Each reviewer independently read 18F-DCFPyL PET/CT patient scans according to a one-reader paradigm, without being informed by either of the other two radiologists and without input from the Truth Panel, the local Investigator, or the Sponsor or designee.

2. Truth Panel assessment was comprised of two distinct independent readers (i.e., not members of the blinded reader group). The Truth Panel readers were blinded to all data generated by the three blinded central 18F-DCFPyL PET/CT readers. The Truth Panel collaborated to provide a consensus read for each patient with correlative imaging and/or biopsy-guided imaging submitted by the local Investigator.

Statistical methods

All efficacy analyses were performed on the full analysis set (FAS), which includes patients who received any amount of 18F-DCFPyL and had 18F-DCFPyL PET/CT imaging results from at least one central reader.

The efficacy was assessed based on the primary endpoint of CLR, a measure of PPV at the patient level that employed anatomic lesion location matching, and a novel composite SOT using histopathology (preferred), correlative imaging, or PSA response to Radiotherapy (RT).

The CLR was computed as TP/(TP+FP)×100% for each 18F-DCFPyL PET/CT central reader across all evaluable patients. The respective two-sided 95% confidence interval (CI) for each reader was computed using the binomial approximation to the normal distribution for each central reader. If the lower bound of the 95% CI was >0.2 for at least 2 of the 3 independent imaging reviewers, then the primary endpoint analysis was considered a success.

A true positive (TP) result was defined as a patient with a positive lesion(s) on 18F-DCFPyL PET/CT evaluated by at least one central reader and a positive result on the composite truth standard. One positive anatomical correlate on histopathology or follow-up imaging sufficed to declare the 18F-

DCFPyL PET/CT assessed by the central reader to be a TP. If a patient had more than one lesion identified by pathology or by correlative imaging, at least one lesion had to be successfully co-localised with the 18F-DCFPyL PET/CT lesion for the patient to be considered a TP. A patient with a positive 18F-DCFPyL PET/CT scan who had the serum PSA response (decline from baseline of ≥50%) following RT as the standard of truth would also be categorized as TP.

A false positive (FP) was defined as a patient with positive lesion(s) on 18F-DCFPyL PET/CT from at least one central reader and with negative findings for prostate cancer according to the composite truth standard.

A patient was considered unevaluable if the patient's 18F-DCFPyL PET/CT scan was interpreted as positive by one or more of the central readers and no evaluable SOT data was available or the lesion location(s) identified on the truth standard did not match a positive lesion location identified by the central 18F-DCFPyL reader(s).

If a patient had an 18F-DCFPyL PET/CT scan that the central reader(s) identified as negative, but the truth standard was positive, the patient was considered a false negative (FN). If a patient had an 18F-DCFPyL PET/CT scan that the central reader(s) identified as negative, and the truth standard was negative, the patient was considered a true negative (TN).

Due to the entry criterion of noninformative standard of care baseline imaging, the majority (67%) of patients had low serum PSA concentrations (<2.0 ng/mL). As such, this BCR cohort of patients may have entered the trial with a lower pre-test probability of detecting disease compared to a general BCR population, demonstrating robust clinical benefit of the efficacy data obtained in CONDOR. Due to the design of the primary endpoint, only patients with locally assessed 18F-DCFPyL-positive lesions were followed for verification. As a consequence, sensitivity analyses of the primary endpoint were performed to account for missing and/or unevaluable SOT data. Multiple imputation and tipping point analyses, as well as re-assigning unevaluable records with centrally-read 18F-DCFPyL positive finding as false positives, all resulted in high CLRs, further supporting the robustness of 18F-DCFPyL PET in achieving the primary endpoint.

As a sensitivity analysis, the analysis of the primary endpoint was repeated for patients in the per protocol (PP) population, the FAS excluding patients with major protocol violations.

The primary endpoint was also analysed for patients who had positive 18F-DCFPyL PET/CT by local interpretation and using lesion locations recorded in the electronic case report form (eCRF).

Pattern mixture model-based multiple imputations (MI) assuming data are missing-at-random (MAR) and a tipping point analysis were performed as sensitivity analyses to examine the influence of the missing or unevaluable standard of truth assessments for patients who had 18F-DCFPyL PET/CT results by a central reader. The locations of lesions identified by the Truth Panel were imputed as the lesion locations in the multiple imputation scenarios.

The primary endpoint was also calculated in subgroups: truth standard category; truth standard of each correlative imaging method; age; race; ethnicity; baseline PSA; historical initial therapy at study entry; baseline screening imaging modality; study center; size of the largest lesion detected on the 18FDCFPyL PET/CT by the central readers; maximum standard uptake value (SUVmax) reported on the 18FDCFPyL PET/CT by the central readers; time of 18F-DCFPyL PET/CT following dosing; time since discontinuation of ADT for patients with prior ADT.

The secondary efficacy endpoint, change in planned medical management, was generated on the FAS and analyzed by calculating a two-sided 95% CI for the proportion of patients with any change in planned management as a binary variable. Shift tables were constructed for changes between no planned treatment and major categories of therapy, between major categories of therapy, and

between categories of local therapy. Changes in planned therapy are also tabulated by the results reported by the central 18FDCFPyL PET/CT readers.

The exploratory endpoint, detection rate, was defined as the percent of positive 18F-DCFPyL PET/CT scans identified by the central imaging readers: (the number of patients with positive scans / the number of patients with reported evaluable scan results) × 100%. Detection rates were calculated for anatomic regions, PSA values by category, and screening imaging modality.

The exploratory endpoint, PPV, was calculated for patients with positive 18F-DCFPyL PET/CT scans as TP/(TP+FP) × 100%. PPV was calculated by anatomic region.

The false positive rate was calculated as (the number of patients with scans defined as positive by the central imaging reader that were not confirmed by a truth standard) / (the number of patients with local positive scan results) × 100%.

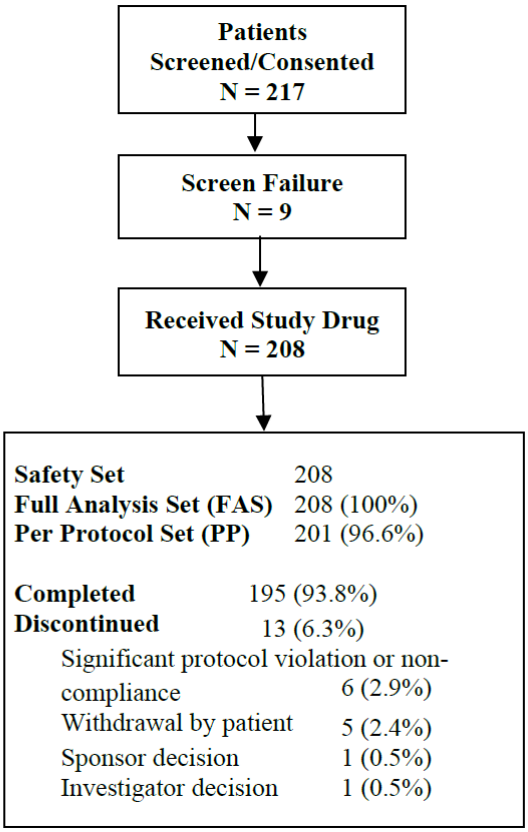
Detection rates, PPV, and false positive rates were analyzed using a two-sided 95% CI presented for each central imaging reviewer and for the local site interpretation separately based on a normal approximation to the binomial.

Results

Participant flow

A total of 217 patients provided informed consent to participate in the study but nine patients there were a screen failure. All the 208 patients who received any amount of 18F-DCFPyL (safety set) underwent PET/CT imaging and had an evaluable 18F-DCFPyL PET/CT imaging result (FAS). Of the 208 patients, 195 (93.8%) completed the study, and 13 (6.3%) discontinued. The reasons for discontinuation were protocol violation or noncompliance (6 patients), withdrawal by patient (5), Sponsor decision (1), and Investigator decision (1). No patients discontinued the study due to an AE.

Figure 7. Patient disposition and Primary Reason for Discontinuation from the Study



Recruitment

Patients were deemed enrolled once they signed the ICF, met all inclusion and no exclusion criteria, and completed all screening assessments. The study duration of patient participation from screening through 18F-DCFPyL PET/CT imaging and Efficacy visit(s), if applicable, was a maximum of approximately 12 months. At a minimum, all patients who received a dose of 18F-DCFPyL were followed from the time of informed consent until the safety phone call on Day 8 (±3). The study was conducted from November 2018 to August 2019, with a first patient enrolled on 27 November 2018 and a last patient enrolled 26 July 2019. The date of the last completed patient is 29 August 2019.

Conduct of the study

The original protocol, dated 31 July 2018, was not amended.

Baseline data

Demographics (safety set)

The study population included men with a mean (SD) age of 67.9 (7.81) years; the majority (67.8%) were 65 years or older and the largest racial groups were white (90.4%) and black or African-American (7.2%); the majority were not Hispanic or Latino (94.2%).

Baseline Disease History and Characteristics

At baseline, and based on last AJCC staging, regional lymph node metastasis was primarily NX or N0 (183, 88%), and all patients had no known distant metastasis (100% with MX or M0). The median baseline PSA was 0.8 ng/mL (range, 0.2 to 98.5 ng/mL). 63% had non-informative whole body bone scan and CT/MRI/fluorodeoxyglucose (FDG) PET, 20% had CT or MRI only, 10% had 18F-fluciclovine or 11C-choline PET (with or without other modalities), and 7% had whole body bone scan only.

Prior Prostate Cancer Treatment

Most patients (177, 85.1%) had prior RP and 105 (50.5%) patients had prior RT; 103 (49.5%) patients had prior RP only, 31 (14.9%) had prior RT only, and 74 (35.6%) had both RP and RT.

Of the 105 patients who had received at least one prior course of RT for prostate cancer, 99.0% had RT to the prostate or prostate bed. External beam radiation therapy (EBRT) was more common than brachytherapy.

Fifty-eight (27.9%) patients had received at least one prior systemic therapy, mostly ADT. The most frequent prostate cancer medications taken prior to study entry included leuprorelin (40, 19.2%), bicalutamide (19, 9.1%), and degarelix (10, 4.8%).

Numbers analysed

Table 23. Patient Enrollment and Disposition (All Patients)

Parameter	All Patients (N=217) n (%)
Consented Set[1]	217
Screen failure[2]	9 (4.1)
Safety Set[3]	208
Full Analysis Set (FAS)[4]	208 (100)
Per Protocol Set[5]	201 (96.6)
Patients completed	195 (93.8)
Patients discontinued	13 (6.3)

Percentages for responses under the consented set are based on the consented set; all others are based on the safety set.

[1] The consented set includes patients who signed an informed consent.

[2] Percentage based on consented set.

[3] The safety set includes all patients who received any amount of 18F-DCFPyL.

[4] The FAS includes patients who received any amount of 18F-DCFPyL and have a 18F-DCFPyL central imaging reader result.

[5] The per protocol set includes the FAS, excluding patients with major protocol violations.

Outcomes and estimation

Primary Efficacy Results (CLR: correct localisation rate)

The primary endpoint of CLR on the patient level met the pre-specified CLR success criterion whereby the lower limit of the 95% CI of the CLR exceeded 20% for at least two of the three independent, blinded central readers.

Overall, 18F-DCFPyL PET/CT imaging detected at least one prostate cancer lesion in 59.1% to 65.9% (n=123 to 137) of patients by the three independent, blinded central readers. The CLR was 85% to 87% and the lower limit of the 95% CI was 78% to 94% among the three readers (see table below).

Table 24: CLR and TP Detection Rate at the Patient Level, CONDOR (FAS)

Assessment of ^{18}F-DCFPyL PET/CT[2]	All Patients (N=208)		
	Reader 1 n (%) (95% CI)[1]	Reader 2 n (%) (95% CI)[1]	Reader 3 n (%) (95% CI)[1]
Negative scan	71 (34.1) (27.7, 40.6)	84 (40.4) (33.7, 47.1)	85 (40.9) (34.2, 47.5)
Positive scan	137 (65.9) (59.4, 72.3)	124 (59.6) (52.9, 66.3)	123 (59.1) (52.5, 65.8)
TP	89 (42.8) (36.1, 49.5)	87 (41.8) (35.1, 48.5)	84 (40.4) (33.7, 47.1)
FP	15 (7.2) (3.7, 10.7)	13 (6.3) (3.0, 9.5)	15 (7.2) (3.7, 10.7)
Unevaluable[3]	33 (15.9)	24 (11.5)	24 (11.5)
No SOT submitted	25 (12.0)	17 (8.2)	17 (8.2)
SOT lesion not matched	8 (3.8)	7 (3.4)	7 (3.4)
CLR	89 (85.6) (78.8, 92.3)	87 (87.0) (80.4, 93.6)	84 (84.8) (77.8, 91.9)

CI=confidence interval; CLR=correct localisation rate for positive scans: FAS=Full Analysis Set; FP=false positive; SOT=standard of truth; TP=true positive. The FAS consisted of patients who received any amount of 18F-DCFPyL and had an 18F-DCFPyL PET/CT central imaging reader result.

[1]Two-sided 95% CI derived from a one-sample binomial distribution.

[2]18F-DCFPyL scans assessed by central readers and then compared to the SOT.

[3]Unevaluable records were due to either an SOT not submitted for central review, or the SOT lesion evaluated did not match any positive 18F-DCFPyL lesion.

CLR by Standard of Truth Method

Histopathology: The CLR for the three readers for patients who had pathology as the SOT (n=31) was 79% (22/28), 83% (24/29), and 81% (21/26).

Correlative Imaging: When correlative imaging was used as the SOT (n=100), CLR for Readers 1, 2 and 3 was 88% (66/75), 89% (62/70), and 86% (62/72), respectively. 18F-fluciclovine PET/CT was the most commonly used method of correlative imaging in 71% of patients. Other modalities included MRI in 23% of patients, CT in 6%, and ultrasound and whole-body scan in 1% each. The CLR for the three readers as verified by 18F-fluciclovine PET/CT was 91% (50/55), 90% (45/50) and 87% (46/53), respectively.

PSA response: For the only one patient who was evaluated by PSA response following RT, all three readers identified 18F-DCFPyL PET/CT positive lesion(s). The patient had a confirmed PSA reduction from 0.80 ng/mL to 0.06 ng/mL at 3 months post-RT, which was confirmed by a value of 0.07 ng/mL one week later.

CLR by Baseline Imaging Modality

CLR was consistently high for all patients grouped by negative baseline imaging modality: from 85.1% to 86.3% for patients who had whole body bone scan and CT/MRI/FDG PET (n=131), 76.2% to 78.9% for patients who had CT or MRI (n=42), 100% for those with negative 18F-fluciclovine or 11C-choline PET (n=20), and 100% for those with negative whole body bone scan only (n=15).

Detection rates ranged from 58.8% to 66.4% for patients with negative whole body bone scan and CT/MRI/FDG PET (n=131), from 47.6% to 71.4% for patients with negative CT or MRI (n=42), from 70.0% to 80.0% for patients who had negative 18F-fluciclovine or 11C-choline PET (n=20), and from 26.7% to 40.0% for patients who only had negative whole body bone scan (n=15).

Table 28 below shows patient-level piflufolastat (18F) PET/CT results from the majority read stratified by serum PSA level. Percent PET positivity was calculated as the proportion of patients with a positive

PET/CT out of all patients scanned. The likelihood of a patient having at least one piflufolastat (18F) PET-positive lesion generally increased with higher serum PSA level.

Table 25. Patient-Level piflufolastat (^{18}F) PET results and percent PET positivity* stratified by serum PSA level in the CONDOR study using majority result among three readers (n=199)**

PSA (ng/mL)	PET positive patients				PET negative patients	Percent PET positivity (95% CI) *
	Total	TP	FP	Unevaluable (Without reference standard)		
< 0.5	24	11	4	9	45	35 (24;46)
≥0.5 and <1	18	12	3	3	18	50 (34;66)
≥1 and <2	21	15	3	3	10	68 (51;84)
≥2	57	50	3	4	6	90 (83;98)
Total	120	88	13	19	79	60 (54;67)

* Percent PET positivity = PET positive patients/total patients scanned. PET positive patients include true positive and false positive patients as well as those who did not have reference standard information.

** Six patients were excluded from this table due to lack of baseline PSA level, and three patients were excluded from this table due to lack of majority result among three readers.

Abbreviations: TP = true positive, FP = false positive, CI = confidence interval

Secondary analysis (Change in Planned Medical Management)

Treating physicians completed pre- and post-18F-DCFPyL PET/CT imaging clinical management questionnaires (MMQs) in a total of 207 of the 208 patients in the FAS (142 [69.3%] with positive 18F-DCFPyL PET/CT scans and 63 [30.7%] with negative scans, and 2 with unevaluable scans) based on local radiology interpretation.

For the 207 patients with an MMQ completed at pre-and post-scanning, 63.9% (131/207) patients had a change in intended management after 18F-DCFPyL PET/CT. Of the patients with changed clinical management plans, 78.6% (103/131) were based on positive PSMA PET/CT findings, and 21.4% (28/131) were based on negative findings. The most frequent changes were from salvage local therapy to systemic therapy (58 patients), from observation to initiating any therapy (49 patients), from noncurative systemic therapy to salvage local therapy (43 patients), and from planned treatment to observation (no treatment) (9 patients).

Intra- and Inter-reader Agreement

The concordance between the central readers, as well as between each central reader and the local reader, was assessed. Central readers were 76% (Fleiss' kappa 0.65 [95% CI 0.58, 0.73]) in agreement with regard to the interpretation of positive or negative 18F-DCFPyL PET/CT scans. The concordance between each central reader and the local reader ranged from 83% to 84%. The intra-reader agreement testing resulted in almost perfect to perfect agreement (Cohen's kappa coefficient ≥0.81) in 18F-DCFPyL PET/CT positivity.

Ancillary analyses

Sensitivity analyses

Several sensitivity analyses were performed for the primary endpoint (CLR) i.e., for the Per Protocol Population, by Local Interpretation of 18F-DCFPyL PET/CT scans, with Unevaluable SOT analysed as FP (False Positive), CLR with lesion location recorded on the CRF and CLR from Multiple Imputation and Tipping Point Analyses.

CLR with Multiple Imputation Methods

Among the sensitivity analyses is included the multiple imputation and tipping point analyses of the CLR for patients with unevaluable SOTs.

The maximum likelihood estimates (MLEs) for the three central readers ranged from 86% to 98%. The CLR estimates and the corresponding 95% CIs from this analysis were consistent with the primary endpoint analysis results. The MLE estimates of CLR ranged from 76% to 80% for histopathology and from 95% to 97% for correlative imaging. The corresponding 95% CIs were consistently high for both histopathology and correlative imaging, similar to the analyses by SOT method.

The results of the tipping point analysis showed that the estimates were lower as the delta values increased, but, for all delta values, the lower bounds of the 95% CI for PPV were above 20%.

Subgroup analysis

Detection rate and CLR by Baseline PSA

Detection rate appeared to increase numerically with higher baseline PSA values based on the analysis subgroups and CLR was consistently high across baseline PSA ranges. In patients with baseline PSA 0.2 to <2.0 ng/mL (n=137), 18F-DCFPyL PET/CT detected PCa in 34% to 73% of patients across the subgroups of 0.2 to <0.5 ng/mL (34% to 42%), 0.5 to <1.0 ng/mL (46% to 57%), and 1.0 to <2.0 ng/mL (58% to 73%).

In patients with PSA ≥2.0 ng/mL (n=63), detection rates ranged from 82% to 97% within the subgroups of 2 to <5 ng/mL (82% to 88%) and ≥5 ng/mL (90% to 97%).

Within the subgroups, CLR was 73% to 85% in patients with PSA 0.2 to <2.0 ng/mL (n=137) and was 91% to 97% in patients with PSA ≥2.0 ng/mL (n=66).

Detection Rate and PPV by Anatomic Region

Detection rate and PPV were calculated at the anatomic region level (prostatic, pelvic, and extrapelvic [ePLNs, bone, and visceral/soft tissue]) for the three independent readers.

Detection rate of 18F-DCFPyL PET/CT for recurrent or metastatic PCa was distributed relatively evenly across the anatomic regions: 18% to 21% for prostatic lesions; 34% to 38% for pelvic lesions; and 26% to 31% for extra-pelvic lesions.

PPV was consistently high in all anatomic regions. In the prostatic region (prostate gland or prostate bed), PPV ranged from 75% to 83.3% among the three readers. In the pelvic region (N stage), PPV was 67.2% to 72.7% among the three readers. In the extra-pelvic region (M stage), PPV was also calculated by extent of metastatic disease: ePLNs, bone, and visceral/soft tissue. For ePLNs (M1a), PPV ranged from 60.9% to 65.2%; for bone metastasis (M1b), PPV ranged from 60.9% to 63.6%, and for the very small number of patients (n=6 to 9) with positive visceral/soft tissue lesions, PPV ranged from 22.2% to 33.3% for visceral/soft tissue metastasis (M1c) based on the SOT, which were almost all correlative imaging. Only one patient had a histopathology of the visceral lesion as the SOT and was confirmed positive for PCa (TP).

PYTHON STUDY (Diagnostic performance and Clinical Impact in BCR patients)

Methods

This was a Prospective, open label, cross-over, comparative study with randomised treatment administration (18F-DCFPyL as an investigational medicinal product, or 18F-Fluorocholine, 18F-FCH, as a comparator) and with randomised central image evaluation.

Study participants

Men≥18 years of age with histologically confirmed prostate adenocarcinoma per original diagnosis, with first suspected recurrence of PCa based on rising prostate specific antigen (PSA) after initial curative therapy. All patients provided informed consent before any study procedures were performed.

Inclusion criteria

1. Male.

2. Age ≥ 18 years.

3. Histopathological proven prostate adenocarcinoma per original diagnosis.

4. First suspected recurrence of PCa based on rising prostate-specific antigen (PSA) after initial curative therapy with radical prostatectomy of PSA ≥0.2 ng/mL confirmed by a subsequent PSA level of ≥0.2 ng/mL or with radiation therapy (external beam or brachytherapy) of PSA > 2 ng/mL above the nadir after therapy regardless of the serum concentration of the nadir.

5. Able and willing to provide informed consent and comply with protocol requirements.

6. Patient who can undergo all study procedures per Investigator's point of view.

7. Patient with social insurance cover.

To note: Inclusion criteria 4 was implemented as it corresponds to common definition of recurrence.

Exclusion criteria

Patients displaying any of the following criteria could not be included:

1. ECOG>2

2. History of previous salvage therapies (including salvage radiotherapy or salvage lymph node dissection).

3. History of adjuvant radiotherapy.

4. History of cryotherapy, high-intensity focused ultrasound (HIFU).

5. Other active malignant tumour.

6. Treatment with Androgen Deprivation Therapy (ADT) in the past 30 days or ongoing.

7. Treatment with colchicine in the past 8 days or ongoing.

8. Treatment with hematopoietic colony stimulating factors (CSF) in the past 5 days or ongoing.

9. Unable to lie supine for imaging.

10. Known allergy to investigational or reference products or to any excipients.

11. Unable to provide written consent (linguistic or psychological inability).

12. Participation in another clinical study within one month prior to inclusion.

13. Uncooperative, in the Investigator's opinion.

14. Subjects deprived of their freedom by administrative or legal decision or who are under guardianship.

To note: Exclusion criteria, 1 to 8 were included as these conditions or past treatments could interfere with the interpretation of PET/CT images. Exclusion criteria, 9 and 11 were included for safety reason.

Treatments

Each patient was planned to receive one single intravenous injection of 330 MBq of 18F-DCFPyL (300-360 MBq) and one single intravenous injection of 18F-FCH at an activity of 2 to 4 MBq/kg body weight (140-280 MBq). The order of administration was randomised. A 10% variation in target activity was allowed. The median decay corrected dose at the time of administration was 321.19 (186.9-373.0) MBq.

The activity of 18F-FCH was the recommended activity mentioned in the approved SmPC. The washout period between the two injections had to range between 24 hours and 12 days.

Patients had not to be fasted before 18F-DCFPyL injection. Patients had to be fasted with no hydric restriction for four hours before 18F-FCH injection.

PET/CT after administration of 18F-DCFPyL as an investigational medicinal product (IMP) and PET/CT after administration of 18F-FCH as a comparator were performed in all patients within a maximum time interval of 12 days.

External independent coded and masked (blinded) interpretations of 18F-DCFPyl PET/CT and of 18F-FCH PET/CT were performed by three independent masked and trained experts who were not otherwise involved in the trial. The order of presentation of PET/CT examination with IMP and with comparator was randomised, and a washout period of 2 weeks between the interpretations of two PET/CT examinations for a same patient was respected.

As part of the routine care practice, these patients received appropriate treatment and follow-up. The investigating sites were therefore requested for the period of up to 10 months after the second tracer injection, to provide any results of subsequent biopsies, imaging studies, clinical findings, PSA measurements, and disease management if performed in routine practice. Treatment decisions were not standardised and made at the discretion of the referring physician based on all available clinical information, including local reports of both PET/CT scans and any other imaging findings.

After completion of the study, a consensus was obtained from a multidisciplinary independent board (truth panel), based on the surrogate standard of reference which included all the above mentioned available results except PET/CT results from 18F-DCFPyL (IMP) and 18F-FCH (comparator). Assessments were made on a per-region and per-patient basis. The truth panel consisted in three independent experts (not otherwise involved in the trial).

All above information was sequentially presented to the truth panel experts. The order of presentation of 18F-FCH PET/CT and 18F-DCFPyL PET/CT results was randomised. The truth panel had to assess the impact of each PET/CT examination on disease restaging and change in treatment intent, by filling in a patient management questionnaire after review of each PET/CT examination report.

Objectives

The primary objective was to compare per-patient detection rate of 18F-DCFPyL PET/CT versus that of 18F-FCH PET/CT (18F-Fluorocholine PET/CT).

Secondary objectives were the assessment of:

-The impact on patient treatment/management.

-The per-region detection rates of 18F-DCFPyL PET/CT versus those of 18F-FCH PET/CT.

-The sensitivity and specificity of 18F-DCFPyL PET/CT versus those of 18F-FCH PET/CT on a per-patient and per-region basis, using a composite SOR.

-The concordance rates between 18F-DCFPyL PET/CT and 18F-FCH PET/CT for regions using a composite standard of references (SOR).

-The safety of 18F-DCFPyL versus that of 18F-FCH.

Outcomes/endpoints

Primary endpoint:

Comparison of the per-patient detection rate for 18F-DCFPyL and 18F-FCH PET/CT.

Secondary efficacy endpoints:

-Comparison of the per-region detection rate[3] for 18F-DCFPyL and 18F-FCH PET/CT.

-Comparison of the sensitivity and the specificity of 18F-DCFPyL PET/CT and of 18F-FCH PET/CT to detect recurrence of PCa on a per-patient basis as well as on a per-region basis in reference to the composite SOR.

-The concordance rate between 18F-DCFPyL PET/CT and 18F-FCH PET/CT on a region basis.

-Comparison of the impact on patient treatment/management for 18F-DCFPyL PET/CT and 18F-FCH PET/CT.

-Safety endpoints: Treatment-emergent adverse events (TEAEs) within 24 h after injection and SAEs during the 10-month follow-up. Change from baseline in clinical laboratory values, and vital signs.

Sample size

The primary efficacy variable is the per-patient detection rate of 18F-DCFPyL PET/CT versus that of 18F-FCH PET/CT.

A review of the available literature on the detection rates for both tracers has been performed. A meta-analysis of Von Eyben et al including 12 publications on the detection rate of 18F-FCH PET/CTreports an overall detection rate of 66.4% (656/987 patients) (Von Eyben et al., 2016). Cimitan M et al report a positive rate of 64.5% in 1,000 patients, who received F-Choline PET/CT in the context of biochemical recurrence of prostate cancer, and were retrospectively analysed (Cimitan et al., 2015]. Gillebert et al report a detection rate of 59% in the French prospective study ICHOROPRO (Gillebert et al., 2018).

[3] Detection rate (DR), number of patients defined as positive at patient level by the independent readers among the total number of patients assessed (for 18F-DCFPyL and 18F-FCH PET/CT)

Three publications report the detection rate of 18F-DCF-PyL PET/CT. The first publication reports a detection rate of 84.6% (110/130 patients) (Rousseau et al., 2019) and the second publication reports a detection rate of 86.3% (214/248 patients) (Wondergem et al., 2019], and the third publication reports a detection rate of 74.2% (46/62 patients) (Dietlein et al., 2017).

The sample size was computed using SAS (Proc Power with the paired freq statement and the Miettinen method) with the following hypothesis:

-Two-tailed risk 1 error (α) = 0.05

-Power (1-β) = 0.9

-Correlation between measure 1 and measure 2 = 0.5

-Detection rate with 18F-Fluorocholine = 0.66

-Detection rate with 18F-DCFPyL = +12% with respect to the reference rate. A difference of+12% between the 18F-FCH and the 18F-DCFPyL being assessed as the minimal clinically expected improvement with respect to results published in the literature (Rousseau et al., 2019).

Number of patients to be randomised to show a significant difference at the 5% level between the detection rate with 18F-Fluorocholine and 18F-DCFPyL:

Detection rate with 18F-Fluorocholine	Expected difference between methods	Detection rate with 18F-DCFPyL	Statistical power =0.9
66%	12%	78%	141

With detection rates of 66% and 78% expected with 18F-Fluorocholine and 18F-DCFPyL respectively, 141 patients will have to be randomised to show a statistical significant difference at the two-sided 5% level with a statistical power of 0.9.

Assuming that 35% of randomised patients will not be assessable, 217 will have to be included.

Randomisation

Eligible patients were randomised in a 1:1 ratio to either the treatment sequence 18F-FCH PET/CT followed by 18F-DCFPyL PET/CT or 18F-DCFPyL PET/CT followed by 18F-FCH PET/CT.

The randomisation was stratified on the type of the previous therapy (radical prostatectomy +/- eLND / curative radiation therapy) and done centrally using an interactive web response system (IWRS).

Blinding

There was no blinding for the administered study drug, as this study is open-labelled.

PET/CT images-Independent blinded readers

An external, coded, masked, and independent interpretation of the 18F-FCH PET/CT and 18F-DCFPyL PET/CT images were performed. Three independent masked and trained readers not otherwise involved in the trial interpreted each PET/CT scans. The order of images presentation was randomised, and a washout period of 4 weeks between the two PET/CT scans for the same patient will be respected. Readers who do not have any knowledge of the following independently evaluated the images of 18F-DCFPyL PET /CT and 18F-FCH PET /CT: patient specific information (history, physical

examination, results of other imaging studies), final diagnosis, treatments, patient outcome and medicinal product used to obtain a given image. Each reader was masked to the interpretations of the other readers.

Patients' first and second scans were separated into two batches. Each batch had to be analysed within a period of four weeks and a washout period of at least four weeks was mandatory between the two batches. 18F-FCH and 18F-DCFPyL PET/CT were separated into different clusters inside a batch. One cluster corresponded to all 18F-FCH cases and the second cluster to all 18F-DCFPyL cases. Indeed, 18F-FCH and 18F-DCFPyL have a different biodistribution and the interpretation criteria are also different. Therefore, the radiotracer could not strictly blinded. Moreover, it was easier for the readers that they could focus on applying consistent analysis for the whole cluster at a time, instead of presenting 18F-FCH and 18F-DCFPyL in a completely randomised sequence. Reader saw both the attenuation-corrected and non-attenuation-corrected PET images at the same time, as well as all the CT images. All the 18F-FCH acquisition sets were presented at the same time. Readers were blinded to all patients' data. Readers were not allowed to see previous assessments. In addition, 10 % of the cases were repeated for the assessment of intra-individual variability. These cases were added into the second batch in a randomised order.

Truth panel

After completion of the study, a consensus was obtained from a multidisciplinary independent board (truth panel) on SOR determination and impact on management. There was two sequential Truth Panel sessions with a washout period of two weeks between the sessions. The first session was aim at SOR determination for each patient. The second session was aim at determination of the impact of the imaging on diagnostic thinking and patient management. The order of presentation of the PET/CT results was randomized.

The truth panel, composed of 3 independent experts (who were neither involved in the study nor in the blinded read sessions) including one board certified urologist, one board certified nuclear medicine physician, and one board certified oncologist was blinded to PET/CT results for SOR determination. For the assessment of the impact on patient management, they had sequential unblinding access to the baseline data, treatment period tracer 1 data, treatment period tracer 2 data, and finally to all follow-up data.

Statistical Methods

The primary efficacy variable was the per-patient detection rate of 18F-DCFPyL PET/CT versus 18F-FCH PET/CT for recurrence (either local, regional or distant), based on the independent central reading. The detection rate was defined as the ratio between the number of patients defined as positive at patient level by at least 2 independent readers, and the total number of assessed patients.

The per-patient detection rate was defined as follows;

$$\frac{\text{Number of patients defined as "Positive" at patient level by the independent readers [a]}}{\text{Total number of patients assessed [b]}}$$

[a] For readings made twice by a same reader (for analysis of variability intra-reader), only the first readers' review was considered

[b] Patients with imputed result were considered as assessed Per-patient detection rates and associated two-sided 95%CI were computed for 18FDCFPyL PET/CT and for 18F-FCH PET/CT.

The Prescott's test was used to assess the difference between the two methods in term of detection.

Blinded evaluation of images

Twelve regions were assessed but only the five following regions were to be described in the results:

(T) Prostate bed

(N) Pelvic lymph node(s)

(M1a) Extra pelvic lymph node(s)

(M1b) Bone

(M1c) Other organ(s)

PET/CT scans were considered positive:

-On a patient basis, if at least one region was rated positive for the patient

-On a region basis, if at least one lesion was positive for the respective region

Every anatomic field were rated on a Likert 5-point-scale using the following criteria: 1, tumour manifestation; 2, probably tumour manifestation; 3, equivocal; 4, probably benign; and 5, benign.

Within-reader variability and Inter-reader reproducibility was investigated as described above (Blinding section). In order to reduce inter-reader variability, the readers were trained and allocated to evaluate the same set of images as part of the development plan.

The variability intra-reader was analysed overall and for each reader with the Cohen's kappa. The variability inter-reader was analysed overall and for each tracer with the Fleiss' kappa.

The **SOR** was made of an appropriate combination of tests available at baseline and performed in clinical routine practice up to 10 months after the last 18F-tracer injection including as described as follows.

Ideally, every lesion detected on imaging should be confirmed by anatomopathological validation. However, histopathology is often lacking (because the location of the lesions is deep within the pelvis and consequently difficult to sample, or the number of lesions is too high and it is not feasible to sample them all individually, or if there are ethical issues regarding the need to perform biopsies for research purposes only, or if there are ethical issues to perform invasive biopsies when the local recurrence is obvious based on imaging). Sometimes, biopsy also fails to depict some tumours (false negative rate).

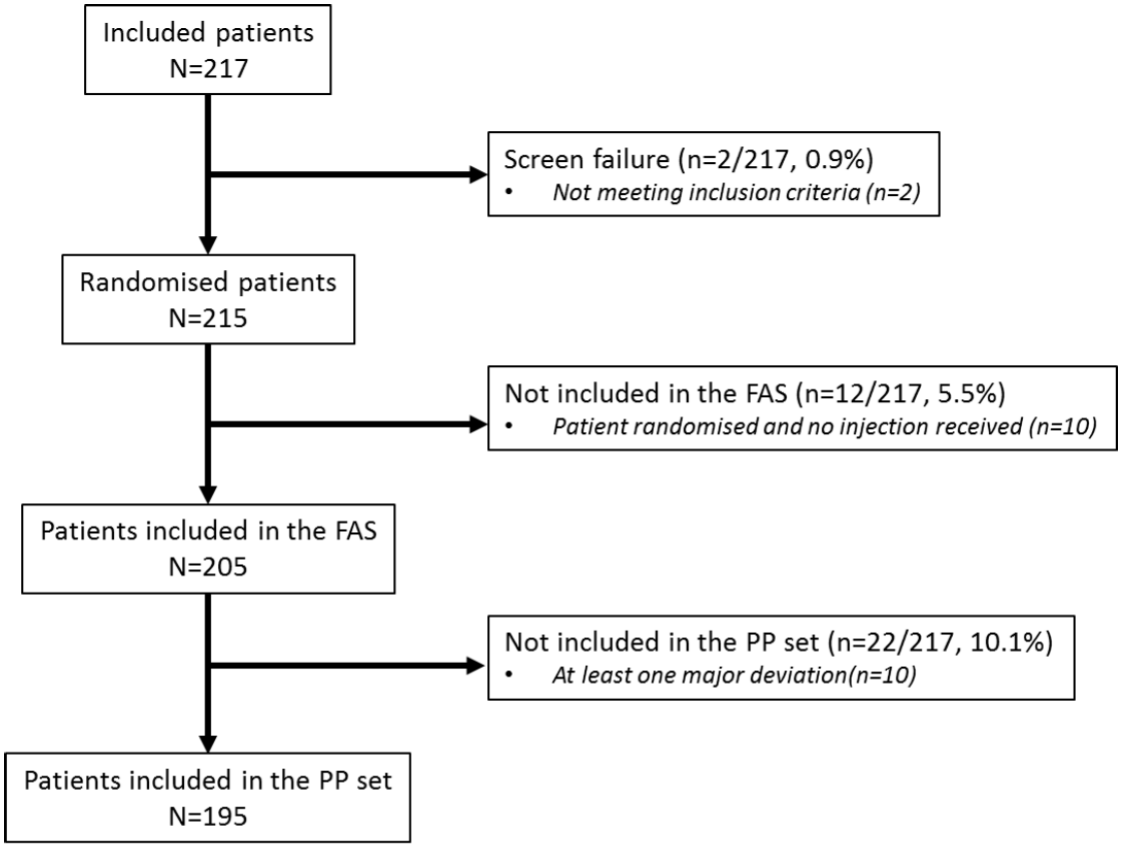
Moreover, patients previously treated with curative surgery presenting with BCR and with negative imaging may be treated with radiation therapy to the prostate bed and/or pelvic LN even without histological proof of local recurrence. Therefore, a consensus was obtained from a multidisciplinary independent board (truth panel), on a surrogate standard of reference (SOR) based on all available data from baseline up to 10-month follow-up performed at the discretion of the physician in regular clinical care practice except PET/CT results. Moreover, the truth panel committee also assessed the impact of each local PET/CT result on disease and patient management.

RESULTS

Participant flow

Overall, 217 patients were included. Among them, 205 (94.5%) patients were included in the FAS. The 12 (5.5%) patients who were not included in the FAS correspond to two patients considered as screen-failure and 10 patients who did not receive any tracer.

Figure 8. Data set analysed



FAS: full analysis set: The full analysis set (FAS) include all randomised patients who received at least one injection of either study product, regardless of any protocol deviations.
PP: per protocol set: The per protocol (PP) set include all patients from the FAS population without any major protocol deviation and who received the required doses of ^{18}F-DCFPyL and ^{18}F-FCH.
Note:
- In this study, the intent-to-treat (ITT) (in this case "intention-to-diagnose") analysis set was the FAS.
- The safety analysis set is confounded with the FAS

Safety analysis set: the safety analysis set included all randomised patients who received at least one injection of either study product (IMP or comparator), regardless of any protocol deviations. The safety analysis set is confounded with the FAS.

Recruitment

The study period lasted from July 2020 until December 2020. The inclusion date of the first patient (first patient first visit, FPFV) was 1 July 2020, and the inclusion date of the last patient (last patient last visit, LPFV) was 4 December 2020 with a Last date of 24h-safety follow-up visit/call after the treatment period tracer 2 on 17 December 2020. The last Truth Panel session occurred on 8 January 2022.

Conduct of the study

The initial approved protocol version was different in each country based on exchanges with competent authorities and ethics committees. A first version (v1.0 of 21 January 2020) was approved and implemented in Spain. A protocol version 2.1 dated 14 May 2020 was approved and implemented in Belgium (with addition of 'Treatment with colchicine in the past 8 days or ongoing' as exclusion criteria, inclusion of PSA kinetics in the subgroup analysis, extension of recruitment period, contraception requirements). Protocol v2.2. dated 4 June 2020 was approved and implemented in France (with change of the name of the sponsor and sites of manufacturing as Curium PET France) followed by a protocol v3.0. dated 4 June 2020 (with some clarifications). Protocol v3.0 dated 15 June 2020 was approved and implemented in Spain (with addition of 2 exclusion criteria respectively 'treatment with colchicine in the past 8 days or ongoing' and 'treatment with hematopoietic colony stimulating factors (CSF) in the past 5 days or ongoing'; some clarifications and harmonization with protocols versions implemented in others MSs). Protocol v3.1 dated 15 June 2020 and protocol v3.2 dated 27 July 2020 were authorized and implemented respectively in Belgium and in the Netherlands to harmonize with protocols versions implemented in others MSs. Protocol v3.3 dated 31 August 2020 was approved and implemented in The Netherlands to add clarification about early termination of the study. Finally, Protocol v4.0 dated 03 March 2021, Protocol v4.1 dated 03 March 2021, and Protocol v4.2 dated 03 March 2021 were authorized and implemented in France and Spain, in Belgium and in the The Netherlands respectively, to extend the follow-up period of the patients from 7 to 10 months.

Baseline data (FAS)

-Patient demographics are presented as follows:

Patients had a median age of 71 (range: 53 to 88) years. The majority were 65 years or older (76.1% in overall FAS population and 77.5% and 74.8% in patients having received first 18F-FCH or 18F-DCFPyL, respectively). The median body mass index (BMI, kg/m²) was 27.39 in the overall population (and similar in both groups 27.85 and 26.84 for patients having received first 18F-FCH or 18F-DCFPyL, respectively). None of the patient presented a BMI<18.5 kg/m². Most of the patients (92.2% [n=189/205]) presented a Grade 0 Eastern Cooperative Oncology Group-Performance Status (ECOG-PS): 96.1% (n=98/102) for patients receiving 18F-FCH first and 88.3% (n=91/103) for patients receiving 18F-DCFPyL first. Few patients (6.8% [n=14/205]) presented a Grade 1 ECOGPS: 3.9% (n=4/102) for patients receiving 18F-FCH first, and 9.7% (n=10/103) for patients receiving 18F-DCFPyL first. The two remaining patients presented a Grade 2 ECOG-PS and were included in the group of patients having received 18F-DCFPyL as first tracer.

PCa history is summarised as follows:

The median time since initial PCa diagnosis was 45.57 months in both groups, ranging from 2.5 to 207.7 months for patients receiving 18F-FCHfirst and from 5.1 to 214.1 months for patients receiving 18F-DCFPyL first. ISUP grade was available for 204 patients (only one missing value in the group of patients receiving 18F-FCH as first tracer). Most of the patients (81.3%) presented with an ISUP grade

from 0-3: Grade 1 was reported for 46 (22.5%), Grade 2 for 74 (36.3%) and Grade 3 for 46 (22.5%). The remaining 18.7%presented with higher ISUP grades: Grade 4 was reported for 23 (11.3%) and Grade 5 for15 (7.4%). D'Amico risk class was available for 204 patients (only one missing value in the group of patients receiving 18F-FCH first). Among them high risk was reported for 79 (38.7%) patients, intermediate risk for 44 (21.6%) patients, and low risk for 25 (12.3%) patients. In addition, D'Amico risk class assessment was not applicable for 56 (27.5%). It corresponds to patients for whom D'Amico risk class was not assessable mainly because of "T" classification of the tumour that was of 3 or over. Regarding tumour, nodes and metastases stage at the time of initial diagnosis of PCa disease, patients were mainly presenting with T2 tumours (121, 60.2%). T3 primary tumour stage was reported in 55 patients (27.4%). Only one patient included in the group having received 18F-DCFPyL as first tracer was presenting with a T4 stage primary tumour. Most patients presented with N0: 124 patients (61.7%). N stage was unknown (Nx) for 66 patients (32.8%). Metastatic status was available for 201 patients. All of them were classified with a M0 disease.

PCa Characteristics at Baseline

The patients were mainly treated with curative intent by RP±eLND (73.2%, n=150/205) and the remaining 26.8% (n=55/205) patients were initially treated with RT. PSA level at first injection was available for 185 patients (90.2%). Among them for patients who were treated initially with RP±eLND: 6 patients (4.4%) with PSA level 2 ng/mL, 71 patients (52.6%) with PSA level ranging from 0.2 to 0.5 ng/mL, 31 patients (23.0%) with PSA level ranging from 0.51 to 1 ng/mL, 18 patients (13.3%) with PSA level ranging from 1.01 to 2 ng/mL and two patients (6.7%) with PSA level >2 ng/mL. These two patients correspond to the two patients who were randomised in the wrong stratum according to previous initial treatment with curative intent. For patients who were treated initially with RT: one patient (2.0%) with PSA level ≤2 ng/mL and 49 patients (98.0%) with PSA level >2 ng/mL. The overall mean time between first abnormal PSA and first PET/CT was of 5.26 months. The mean PSA doubling time (PSAdt) was of 10.80 months. In addition, most of the patients presented with a PSAdt over 6 months was 57.6% (n=102/177). The mean PSA velocity was of 5.45 ng/mL/year.

Prior Systemic Prostate Cancer treatments: Regarding hormonotherapy, 27 patients were treated with androgen deprivation therapy (ADT). Mean treatment duration was of 13.08 [0.0-42.5] months. In addition, three patients, respectively, were treated with another hormonotherapy (no precision was recorded).

Numbers analysed

217 patients were screened and included, 215 patients were randomized. 205 patients received one tracer (18F DCFPyL or 18F-FCH) and 201 patients received both tracers. The FAS (ITT) includes therefore 205 patients (having received at least one injection of either study product, regardless of any protocol deviations). The safety analysis set is confounded with the FAS (205 patients). The PP includes 195 patients (all patients from the FAS population without any major protocol deviation and who received the required doses of 18F-DCFPyL and 18F-FCH).

Outcomes and estimation

PYTHON was a randomised, open-label, two-treatment cross-over study. It enrolled 217 male patients with first biochemical recurrence of prostate cancer, who underwent definitive therapy (radical prostatectomy (RP) ± extented lymph node dissection (eLND) in 73.2% patients, EBRT or brachytherapy in 26.8% patients).

Primary endpoint results

The primary endpoint was detection rate (DR) defined as number of patients defined as positive at patient level by the independent readers among the total number of patients assessed (for piflufolastat (18F) PET/CT and fluorocholine (18F) PET/CT). A significant difference of 12% detection rate in favour of piflufolastat (18F) against Fluorocholine (18F) was pre-defined.

Per-Patient Detection rate (DR)

Overall, per-patient detection rate is summarised in the following table.

Table 26: Per-Patient Detection Rate

Per-Patient Detection Rate	^{18}F-DCFPyL N = 205	^{18}F-FCH N = 205	P-value [a]
Worst case imputation	58.0% (n=119) [95% CI 51.3; 64.8]	40.0% (n=82) [95% CI 33.3; 46.7]	<0.0001
Best case imputation	62.0% (n=127) [95% CI 55.3; 68.6]	42.4% (n=87) [95% CI 35.7; 49.2]	<0.0001
Observed case	58.2% (n=117) [95% CI 51.4; 65.0]	40.3% (n=81) [95% CI 33.5;47.1]	<0.0001

CI=confidence interval. Worst case imputation: missing or indeterminate results were imputed to 'Negative'. Best case imputation: missing or indeterminate results were imputed to 'Positive'. Observed case: missing or indeterminate results were not imputed. As the Prescott's test is only applicable for patients who completed the entire treatment sequence (and in this analyse no imputation is performed), patients with only one injection were not taken into account. [a] P-value issued from Prescott's test.

Detection rate in different subgroups.

Overall, when considering the detection rate in the different subgroups in the observed case, the performance of detection of the 18F-DCFPyL over the 18F-FCH seemed to be apparently higher for all subgroups (PSA level, PSAdt, D'Amico risk and ISUP grade).

Two-hundred one patients performed one piflufolastat (18F) PET/CT and one fluorocholine (18F) PET/CT from mid-thigh to skull vertex in a randomised order. Three independent central readers, blinded to all clinical information, evaluated each piflufolastat (18F) and each fluorocholine (18F) PET/CT for the presence and location of positive lesions. Location of each lesion was categorized into 5 regions (prostate/prostate bed, pelvic lymph nodes, other lymph nodes, bone, soft tissue). Recurrence was detected by the blind read experts in 119 (60.4%) and 82 (41.0%) of the patients with piflufolastat (18F) and fluorocholine (18F) PET/CT, respectively. Details of overall independent reader's interpretation by PSA level is given in Table 30.

Table 27. Per-patient detection rate of PET/CT by PSA level in PYTHON study (N=201)

PSA (ng/mL) level at first injection	piflufolastat (^{18}F)	fluorocholine (^{18}F)
PSA < 0.2 (n=6)	2 (33.3%)	1 (16.7%)
PSA [0.2 - 0.5] (N=68)	24 (35.3%)	21 (30.9%))
PSA [0.51 - 1] (N=31)	17 (54.8%)	10 (32.3%)
PSA [1.01 - 2] (N=19)	13 (68.4%)	6 (31.6%)
PSA >2 (N=57)	50 (87.7%)	39 (68.4%)

Secondary endpoint results

Secondary endpoints were sensitivity (ratio between the number of patients defined as positive for a given region by the independent readers and the total number of patients assessed as positive for a given region by the truth panel), concordance (ratio between the number of regions defined as positive by both piflufolastat (18F) PET/CT and Fluorocholine (18F) PET/CT + the number of regions defined as negative by both piflufolastat (18F) PET/CT and Fluorocholine (18F) PET/CT and the total number of assessed regions) and impact on patient management.

Per-Region Detection rate Overall

Overall, the detection performance of 18F-DCFPyL was better than the performance of 18F-FCH in the prostate bed, bones and other organs. Otherwise, 18F-DCFPyL did not seem to perform better than 18F-FCH in disease detection in the pelvic and ePLNs.

Table 28: Per-Region Detection rate Overall

Region	Per-Region Detection Rate (Observed Case) [95% CI]	
	^{18}F-DCFPyL N = 201	^{18}F-FCH N = 201
(T) Prostate bed	43 (21.4%) [15.7; 27.1]	22 (10.9%) [6.6; 15.3]
(N) PLNs	58 (28.9%) [22.6; 35.1]	50 (24.9%) [18.9; 30.9]
(M1a) ePLNs	16 (8.0%) [4.2; 11.7]	29 (14.4%) [9.6; 19.3]
(M1b) Bone	35 (17.4%) [12.2; 22.7]	17 (8.5%) [4.6; 12.3]
(M1c) Other organ(s)	18 (9.0%) [5.0; 12.9]	4 (2.0%) [0.1; 3.9]

CI=confidence interval; ePLN=extra-pelvic lymph node; PLN=pelvic lymph node.

Per-patient sensitivity and specificity:

Per-patient sensitivity was assessed for 37 patients with a standard of truth and is reported in Table 32. Per-patient sensitivity of (^{18}F)-piflufolastat was significantly higher than that of (^{18}F)-fluorocholine ($p<0.0001$).

Table 29. Per-patient sensitivity (n=37)

PET/CT	piflufolastat (^{18}F)	fluorocholine (^{18}F)
Sensitivity (95% CI)	58.3% (95% CI 51.5;64.9)	40.6% (95% CI 34.1;47.5)

Specificity was considered as not assessable as all patients were assessed as "positive" (i.e., recurrence detected in all patients) by the truth panel experts.

Concordance rate:

The concordance rate between 18F-piflufolastat PET/CT and 18F-fluorocholine PET/CT according to central blind readers, per-region was remarkably high for all regions of interest, namely prostate bed: 87.3% (81.9; 91.3), pelvic lymph nodes: 73.9% (67.3; 79.5), extrapelvic lymph nodes: 86.5% (81.0; 90.6), bones: 86.9% (81.5;91.0), and other organs: 92.0% (87.3; 95.1).

Discordance between 18F-DCFPyL and 18F-FCH were analysed per-region using the SOR when available. Overall, according to the Truth Panel experts the results obtained with 18F-DCFPyL were considered as true in 65% of the cases (26/40). When considering each region independently, results obtained with 18F-DCFPyL were considered as true (positive or negative) by the Truth Panel experts:

-For the prostate bed, in 6/7 cases (85.7%)

-For the lymph nodes, in 8/11 cases (72.7%)

-For the ePLNs, in 100% of the cases (5/5)

-For the bones, in 7/15 (46.7%)

-For other organs, in 0/3 (0%)

Impact on Diagnostic Thinking and Patient Management:

Overall, the Truth Panel considered that patients were mainly presenting with local disease (n=131, 63.9%). Forty patients (40) (19.5%) presented a regional extension and 34 patients (16.6%) presented distant metastases.

The impact on patient management was assessed by the Truth Panel in two different ways.

First, the truth panel determined management based on baseline data and without knowing the results of the PET/CTs. Then they proposed a patient management after reviewing the results of each of the individual PET/CTs (PET/CT being proposed blindly). The truth panel followed a process of evaluation in different subsequent steps. The percentage of changes between the proposed management at baseline and the proposed management after each PET/CT, in this case, represents the impact of each of the PET/CTs images on patient management according to the truth panel management plans. The truth panel proposed to modify treatment intent in 26.0% (n=53/204) and 21.3% (n=43/202) for 18F-DCFPyL and 18F-FCH, respectively.

In a second approach, the truth panel determined management based on baseline data and without knowing the results of the PET/CTs and compared it with the treatment implemented locally by the Investigator who considered the common information of the two PET/CTs since the Investigator was aware of the results of both PET/CTs at the time of the choice of management. The calculated impact is the result of the combination of the two PET/CTs. The truth panel then retrospectively identified the PET/CT examination that had been the most informative at the time of the therapeutic decision locally.

According to the truth panel, the patient management proposed by local team was impacted by the PET/CTs in 48.8% of the cases (100/205 patients), as follows:

• Impact of the 18F-DCFPyL in 44.1% (90/204)

• Impact of 18F-FCH in 28.7% (58/202)

Detection Rate Intra-Reader Variability and Inter-Reader Variability

When considering per-patient detection rate by reader only considering the observed cases Readers 1 and 3 reported a 64.2% and 66.7% positive detection rate for 18F-DCFPyL when Reader 2 only reported a 55.2% positive detection rate. All the readers were consistent when considering positive detection rate for 18F-FCH ranging from 41.3% to 44.3%.

The overall percentage of agreement was of 76.7% with a Cohen's Kappa (95% CI) of 0.54 (0.39; 0.68). These low values of percentage of agreement and of Cohen's Kappa (95% CI) was due to Reader 3. Indeed, this reader reported a 67.5% percentage of agreement and only a Cohen's Kappa (95% CI) of 0.33 (0.05; 0.62). On the contrary, Reader 1 and 2 obtained a percentage of agreement ≥80% (82.5% and 80.0%, respectively) with a Cohen's kappa of 0.64 (0.40; 0.88) and 0.62 (0.39; 0.84) considered to be substantial according to Landis and Koch classification (Landis et al., 1977).

The inter-reader percentage of agreement was of 67.8% and 65.4% for 18F-DCFPyL and 18F-FCH, respectively. The corresponding Fleiss' kappa was of 0.55 (0.47; 0.63) and 0.54 (0.45; 0.63), respectively, indicating a moderate agreement between readers according to Landis and Koch classification (Landis et al., 1977).

Efficacy of 18F-DCFPyL from the literature

The applicant carried out a literature search in 3 databases: PubMed, SCOPUS and Cochrane, from December 2011 to May 2022. Database lock point: 27th May 2022.

"18F-DCFPyL" or "[18F]DCFPyL" or "DCFPyL" or "piflufolastat F-18" or "piflufolastat (18F)" in all fields: Title, abstracts, keywords. The searches resulted in 248 hits.

Each publication was evaluated for relevance based on the title, the abstract or, if still uncertain, on the complete article. More than 100 relevant publications on 18F-DCFPyL were included in the clinical overview, among them 36 studies on efficacy performed in a series of patients.

The applicant presented data from literature on efficacy of 18F-DCFPyL in localisation of primary PCa. These data were not taken into account, as this indication is not claimed in the submitted dossier.

Only the following four studies were submitted for initial staging.

Table 30. Literature references submitted for initial staging

Ref.	Number of patients	Setting	Patient preparation Activity of 18F- DCFPyL administered Adquisition time after 18F-DCFPyL administration	SOT	Parameter evaluated: Detection Rate % (N), Sensitivity % (N) or Specificity % (N) of 18F-DCFPyL
Gorin et al., 2018 Design: prospective study	25	High and very high risk PCa prior RP + PLND with negative conventional imaging N, M staging	NA 333 MBq 60 minutes	Histo-pathology	**Detection rate** Primary PCa: 100% (25/25) **Sensitivity** N staging; N1 disease: 28% (7/25) -Per patient LN; sensitivity: 71.4% (5/7) -Per region LN; sensitivity: 66.7% M staging; M1 disease: 12% (3/25) **Specificity** N staging -Per patient LN; specificity: 88.9% (16/18) -Per region LN; specificity: 92.7% M staging; M1 disease: -
Jansen et al., 2021 Design: prospective study	117	Intermediate and high risk PCa prior RP + ePLND Lymph-node metastases histologically diagnosed in 14.5% (17/117)	NA 311 (IQR 297-324) MBq 118 (IQR 112-123) minutes	Histo-pathology	**Detection rate** N staging; 99.1% (116/117) **Sensitivity** N staging; -Per patient LN; sensitivity: 41.2% (7/17) -Per region LN; sensitivity: 34.7% **Specificity** N staging -Per patient LN; specificity: 94% (103/110) -Per region LN; specificity: 97.7%

Ref.	Number of patients	Setting	Patient preparation Activity of 18F- DCFPyL administered Adquisition time after 18F-DCFPyL administration	SOT	Parameter evaluated: Detection Rate % (N), Sensitivity % (N) or Specificity % (N) of 18F-DCFPyL
Wondergem et al., 2018 Design: retrospective study	133	PCa	NA NA NA	For lymph nodes: imaging	**Detection rate** Primary PCa: 97.8% (n=131/133) Locoregional LN: 51.5% (69/133) Distant LN: 21.6% (29/133) Bones: 26.9% (36/133)
Wondergem et al., 2021 Design: retrospective study	160	High-risk PCa	NA 328 (239-378) MBq 120 minutes	For lymph nodes: imaging	**Detection rate** Primary PCa: 98.1% (157/160) Locoregional LN: 49% (78/160) Distant LN: 28% (44/160) Bones: 31% (49/160) Visceral: 3% (4/160)

AUC=area under the curve; CI=confidence interval; CT=computed tomography; GS=Gleason score; 18F-DCFPyL=(2*S*)-2-[[(1*S*)-1-carboxy-5-[(6-(18F)fluoranylpyridine-3-carbonyl)amino]pentyl]carbamoylamino]pentanedioic acid; MRI=magnetic resonance imaging; LN=Lymph node(s); mpMRI=multiparametric MRI; n=number; NPV=negative predictive value; p=probability; PCa=PCa; PET=positron emission tomography; PPV=positive predictive value; PSA=prostate specific antigen; PSMA=prostate-specific membrane antigen; RP=radical prostatectomy; SOT=standard of truth; SUV=standardised uptake value

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 31. Summary of Efficacy for trial OSPREY

Title: A PrOspective Phase 2/3 Multi-Center Study of 18F-DCFPyL PET/CT Imaging in Patients with PRostate Cancer: Examination of Diagnostic AccuracY (OSPREY)			
Study identifier	PyL2301 – NCT02981368		
Design	Prospective, non-comparative, multicentre, multi-reader, phase 2/3, open-label study, with a fixed dose of 330 MBq.		
	Duration of main phase:		19 months
Hypothesis	Superiority		
Treatments groups	Cohort A : primary staging of PCa		One single injection of 330 MBq
	Cohort B : recurrence of PCa		One single injection of 330 MBq
Endpoints and definitions	Co-Primary endpoint	Sp_{Prim}	Specificity of 18F-DCFPyL PET/CT imaging to determine the absence of metastatic prostate cancer within the pelvic lymph nodes relative to histopathology in patients meeting criteria for inclusion in Cohort A.
		Se_{Prim}	Sensitivity of 18F-DCFPyL PET/CT imaging to determine the presence of metastatic prostate cancer within the pelvic lymph nodes relative to histopathology in Cohort A
	Secondary endpoint	Se_{Sec}	Sensitivity of 18F-DCFPyL PET/CT imaging to detect prostate cancer within sites of metastasis or local recurrence relative to histopathology in Cohort B.
	Secondary endpoints (Cont'd)	PPV_{Prim}	Positive predictive value of 18F-DCFPyL PET/CT imaging to predict the presence of prostate cancer within the prostate gland and lymph nodes in Cohort A.
		NPV_{Prim}	Negative predictive value of 18F-DCFPyL PET/CT imaging to predict the absence of prostate cancer within the prostate gland and lymph nodes in Cohort A.
		PPV_{Sec}	Positive predictive value of 18F-DCFPyL PET/CT imaging to predict prostate cancer within sites of local recurrence and other metastatic lesions in Cohort B
Database lock	17th September 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS) The FAS in Cohort A includes those patients who received 18F-DCFPyL, had a prostatectomy or lymphadenectomy, and provided a 18F-DCFPyL PET image result (positive or negative) and a corresponding histopathology result (positive or negative). The FAS in Cohort B includes those patients who received 18F-DCFPyL, underwent a conventional image-guided biopsy, and provided an 18F-DCFPyL PET image result (positive or negative) and a corresponding histopathology result (positive for prostate cancer or negative), along with a conventional image that confirmed the location of the histopathology sample. Time point: after completion		
Descriptive statistics and estimate variability	Treatment group	Cohort A primary staging of PCa	Cohort B recurrence of PCa
	Number of subject	268	117
	Sp $_{Prim}$	Percentage (95% CI) 96.3-98.9 (93.6-99.4)	
	Se $_{Prim}$	Percentage (95% CI) 30.6-41.9 (19.2-54.2)	
Notes			

Analysis description	**Secondary analysis** The conduct of the analysis was pre-specified		
Descriptive statistics and estimate variability	Treatment group	Cohort A primary staging of PCa	Cohort B recurrence of PCa
	PPV $_{Prim}$	Percentage (95% CI) 75.0-89.5 (58.9-98.3)	
	NPV $_{Prim}$	Percentage (95% CI) 91.3-93.5 (87.4-96.9)	
	Se $_{Sec}$		Percentage (95% CI) 92.9-98.6 (84.0-100)
	PPV $_{Sec}$		Percentage (95% CI) 81.2-87.8 (72.9-95.3)
Notes			

Table 32. Summary of efficacy for trial CONDOR

Title: A Phase 3, Multi-**C**enter, **O**pen-Label Study to Assess the Diag**N**ostic Performance and Clinical Impact of ^{18}F-**D**CFPyL PET/CT Imaging Results in Men with Suspected Recurrence of Pr**O**state Cance**R** (**CONDOR**)			
Study identifier	Pyl3301 NCT03739684		
Design	Phase 3, non-comparative, multi-center, open-label, single-arm, non-randomized study		
	Duration of main phase:		9 months
Hypothesis	Superiority		
Treatments groups	One single group of recurrence of PCa		One single injection of 330 MBq
Endpoints and definitions	Primary endpoint	CLR	The correct localisation rate (CLR) at the patient level, defined as the percentage of patients for whom there was a one-to-one correspondence between localization of at least one lesion identified on 18F-DCFPyL PET/CT imaging and the composite truth standard. CLR=TP/(TP+FP) × 100% for each ^{18}F-DCFPyL PET/CT central reader across all evaluable patients
	Secondary endpoint	IMP	Impact on patient management (IMP) defined as the percentage of patients with a change in intended prostate cancer treatment plans due to ^{18}F- DCFPyL PET/CT as measured by comparison of intended management questionnaires completed pre- and post-^{18}F-DCFPyL PET/CT imaging results

	Exploratory endpoints	DR	The detection rates (DR) of ^{18}F-DCFPyL PET/CT among lesion locations i.e., prostatic, pelvic, extra-pelvic
		PPV	The positive predictive value (PPV) of ^{18}F-DCFPyL PET/CT for prostatic, pelvic, extra-pelvic regions from the composite truth standard in patients with positive lesion(s) on ^{18}F-DCFPyL PET/CT imaging.
		FP	False positive rate (FP) defined as the percentage of patients with positive ^{18}F-DCFPyL PET/CT scans who had negative findings for prostate cancer based on the composite truth standard
		DR by PSA	The detection rates of ^{18}F-DCFPyL PET/CT imaging as a function of baseline PSA groups
Database lock	31st October 2019		

Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	Full Analysis Set (FAS) which includes patients who received any amount of ^{18}F-DCFPyL and had ^{18}F-DCFPyL PET/CT imaging results from at least one central reader. Time point: after completion	
Descriptive statistics and estimate variability	Treatment group	Single group
	Number of subject	208
	CLR Percentage	84.8-87.0

	variability statistic 95%CI	77.8 – 93.6
Notes		
Analysis description	**Secondary analysis** The analysis was pre-specified	
Descriptive statistics and estimate variability	Treatment group	Single group
	Number of subject	208
	IMP Percentage	63.9
	variability statistic 95%CI	56.9 – 70.5
Analysis description	**Exploratory analysis** The analysis was pre-specified	
Descriptive statistics and estimate variability	Treatment group	Single group
	Number of subject	208
	DR Percentage	Prostate level : 17.8 – 21.2 Pelvic region : 33.7 – 37.5 Extra-pelvic region : 25.5 – 31.3
	variability statistic 95%CI	Not available
	PPV Percentage	Prostate level : 75.0 – 83.3 Pelvic region : 67.2 – 72.7 Extra-pelvic region : 67.3 - 69.8
	variability statistic 95%CI	Prostate level : 60.9 – 95.5 Pelvic region : 55.4 – 84.5 Extra-pelvic region : 53.8 - 83.5

Notes	

Table 33. Summary of efficacy for trial PYTHON

Title: A Prospective Study on ^{18}F-DCF**Py**L PE**T**/CT Imaging in Bioc**h**emical Recurrence of Pr**o**state Ca**n**cer (PYTHON)			
Study identifier	PYTHON EudraCT number 2020-000121-37		
Design	Prospective, multicentre, phase 3, open-label, cross-over, order of injection randomised, central image evaluation, order of blinded read sessions randomized study		
	Duration of main phase:		18 months
Hypothesis	Superiority		
Treatments groups	One single group (cross-over design)		One single injection of 330 MBq. Randomisation of the order of products administrations
Endpoints and definitions	Primary endpoint	DR	Detection rate (DR): number of patients defined as positive at patient level by the independent readers among the total number of patients assessed (for ^{18}F-DCFPyL and ^{18}F-FCH PET/CT)
	Secondary endpoint	Se	Sensitivity (Se) rRatio between the number of patients defined as positive for a given region by the independent readers and the total number of patients assessed as positive for a given region by the truth panel
		CONC	Concordance (CONC): ratio between the number of regions defined as positive by both ^{18}F-DCFPyL PET/CT and ^{18}F-FCH PET/CT + the number of regions defined as negative by both ^{18}F-DCFPyL PET/CT and ^{18}F-FCH PET/CT and the total number of assessed regions

		IMP	Impact on patient management (IMP): any change in treatment intent assessed by the truth panel after each examination (18F-DCFPyL PET/CT and 18F-FCH PET/CT).
Database lock	21st February 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS) All randomised patients who received at least one injection of either study product (IMP or comparator), regardless of any protocol deviations. Time point: after completion		
Descriptive statistics and estimate variability	Number of subject	205	
	DR percentage	58.2	
	Two-sided 95% CI	51.4 – 65.0	
Effect estimate per comparison	Primary endpoint DR Percentage (95%CI)	18F-DCFPyL Study drug	18F-FCH Comparator
		58.2	40.3
		51.4-65.0	33.5-47.1
		P-value (Prescott's test)	P<0.0001
Notes			
Analysis description	**Secondary analysis** The analysis was pre-specified		
	Treatment group	18F-DCFPyL	18F-FCH

Descriptive statistics and estimate variability	Number of subject	205	
	Se Percentage 95% IC	Prostate level : 50.0 (30.0-70.0) Pelvic region: 50.0 (25.5-74.5) Extrapelvic region: 66.7 (20.5-93.8)	Prostate level : 30.0 (14.5-52.2) Pelvic region: 41.7 (19.4-68.1) Extrapelvic region: 66.7 (20.5-93.8)
Effect estimate per comparison	P value	Prostate level : NS Pelvic region: NS Extrapelvic region: NS	
Descriptive statistics and estimate variability	CONC Percentage 95% IC	Prostate level : 87.3 (81.9-91.3) Pelvic region: 73.9 (67.3-79.5) Extrapelvic region: 86.5 (81.0-90.6)	
	variability	Descriptive analysis	
Descriptive statistics and estimate variability	IMP percentage	44.1	
	variability	Descriptive analysis	

2.6.5.3. Clinical studies in special populations

There were no dedicated clinical studies by gender and in children submitted as this medicinal product is only intended for adult men.

Moreover, no dedicated studies in patients with renal or hepatic impairment were submitted. Out of total 385 patients in OSPREY, 245 had mild kidney insufficiency, 29 had moderate kidney insufficiency and 1 had severe kidney insufficiency (See 2.6.2.1.).

Regarding the age, the demographics by indication in the 3 main sponsored studies are shown as follows.

1. Initial staging: In Cohort A the demographics by age at informed consent in years were:

Mean age (SD): 64.0 (6.7), Median (Min, Max): 65 (46, 84), Age <65 years, n (%): 132 (49.3) and Age ≥65 years, n (%): 136 (50.7).

2.- Demographics for recurrent or metastatic PCa is shown in the following table.

Table 34. Demographics, Recurrent or Metastatic PCa

Parameter[1]	PYTHON Safety Set (N=205)	OSPREY Cohort B Safety Set (N=117)	CONDOR Safety Set (N=208)
Age at informed consent (years)			
Mean (SD)	70.0 (7.1)	67.9 (7.9)	67.9 (7.8)
Median (Min, Max)	71 (53, 88)	68 (45, 86)	68 (43, 91)
Age <65	49 (23.9)	39 (33.3)	67 (32.2)
Age ≥65	156 (76.1)	78 (66.7)	141 (67.8)

Max=maximum; Min=minimum; ND=not done; PCa=prostate cancer; SD=standard deviation. [1]All patients were men. Percentages are based on the Safety Set for each study, which includes all patients who received any amount of 18F-DCFPyL.

2.6.6. Discussion on clinical efficacy

The claimed indications are 1) initial staging of prostate cancer in patients at risk of metastases who are candidates for definitive therapy, and 2) for localisation of recurrence in case of rising serum PSA levels after treatment.

The applicant has submitted clinical data from three studies to demonstrate efficacy of 18F-DCFPyL PET/CT for diagnostic use in patients with PCa (Osprey, Condor and Python studies). Additionally, the applicant has submitted data from literature to support the efficacy claims. Data from literature and its content is acceptable for this submission.

Overall, the applicant has followed the requirements stated out in the guideline on clinical evaluation of diagnostic agents (Doc. Ref. CPMP/EWP/1119/98/Rev. 1) and the appendix 1, to address the main topics assessing the benefits of diagnostic agents. Mainly, technical performance, diagnostic performance and the impact on patient management have been addressed.

The recommended method for PET images interpretation with piflufolastat (^{18}F) PET/CT is the visual interpretation.

The PET acquisition is performed from mid-thigh through the vertex of the skull, starting 90 to 120 minutes after tracer injection. It must include lower extremities if there is known or suspected disease. Image acquisition duration is 12 to 40 minutes depending on the type of PET cameras, number of bed positions (typically 6 to 8) and acquisition time per bed position (typically 2 minutes to 5 minutes). If

the acquisition leads to indeterminate findings, and provided a sufficient activity remains for adequate counting statistics, late acquisitions can also be performed, thus reducing background activity (see SmPC section 4.2).

The patient should be well hydrated before the start of the examination and urged to void before the examination in order to reduce bladder activity and as often as possible during the first hours after the examination in order to reduce radiation exposure. Systematic use of diuretics is not recommended but may be useful in certain situations to improve quality imaging. A diuretic expected to act within the uptake time period may be administered to improve interpretation of piflufolastat (18F) PET/CT as it results in less activity depositions in ureters and the bladder (see SmPC section 4.4). Low-dose CT has been utilized in the clinical studies for anatomic correlation and attenuation correction. This is correct to not jeopardize the diagnostic performance of 18F-DCFPyL PET. No MRI has been used in the submitted clinical trials, therefore, it is not recommended in SmPC.

Lesions should be considered suspicious if uptake is greater than physiologic uptake in that tissue or greater than adjacent background if no physiologic uptake is expected.

The performance of piflufolastat (18F) for imaging of patients with biochemical evidence of recurrence of prostate cancer seems to be affected by serum PSA levels (see SmPC section 4.4. and 5.1). The performance of piflufolastat (18F) for imaging of metastatic pelvic lymph nodes prior to initial definitive therapy seems to be affected by risk factors such as Gleason score. To date no outcome data exist to support subsequent management of patients based on PSMA-PET in the primary staging. Therefore, treatment should not be changed based on piflufolastat (18F) PET/CT findings only.

Piflufolastat (18F) has not been studied in patients with hepatic impairment and has only been studied in patients with mild renal impairment. No adaptation for administered activity and time for image acquisition is considered necessary in moderate or severe renal insufficiency. However, careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients with severe impaired renal function (see SmPC section 4.2).

Dose response studies

No formal dose-response study has been submitted with this application.

The selection of the dose and optimal imaging timepoint have been based on several pillars, such as radiation dose optimization (ALARA (As Low As is Reasonably Achievable) principle), image quality and current 18F-FDG dose recommendations (Szabo et al., 2015). A high-quality PET image is one in which the proportion of true counts is maximized while minimizing noise. This value is commonly referred to as the Noise Equivalent Count Rate (NECR). Moreover, there is extensive experience from the majority of the published studies in patients with PCa and recommendations from the EANM standardised reporting guideline for PSMA-PET (Ceci et al., 2017). The approach for dose finding is acceptable. The applicant has proposed the dose by BW to be aligned with the majority of diagnostic radiopharmaceuticals. Across clinical development the dose of 333 MBq (single IV dose) was selected to be in line with both the ALARA principle and current 18F-FDG dose recommendations (Szabo et al., 2015). A further analysis was made across all 3 pivotal studies (PYTHON, OSPREY, CONDOR) showing that the mean injected activity per kilogram of body weight and the median activity were quite homogeneous across the 3 studies: mean activity of 3.87 MBq/kg. In accordance with the EMA guideline on core SmPC and package leaflet for radiopharmaceuticals (2011) which recommends a suggested activity range based on a patient of average weight (70kg), expressed in MBq and in round numbers, the mean recommended activity of (18F) piflufolastat is 4 MBq/kg of body weight and can vary from 3 to 5 MBq/kg of body weight depending on the PET equipment and acquisition mode used.

The minimum activity should not fall below 190 MBq and the maximum activity should not exceed 360 MBq.

Main clinical studies

The presented clinical data come from multicentre and prospectively designed studies. Osprey and Condor studies were single-arm, open label studies conducted in USA and Canada. Similar clinical practices on PCa management in USA/Canada and EU justify the extrapolation of data generated with the Osprey and Condor population to the European population.

Osprey study included men at high risk of PCa planned to undergo radical prostatectomy (RP) with pelvic lymph node dissection (PLND). The co-primary endpoints were specificity and sensitivity in cohort A (n=268).

Condor study included 208 men with biochemically recurrent prostate cancer and negative or equivocal conventional imaging. The primary endpoint was the correct localisation rate (CLR) at the patient level.

Python study was a study performed in Europe. It was a cross-over and randomised study to demonstrate superiority on per-patient detection rate (DR) of 18F-DCFPyL PET/CT versus 18F-FCH PET/CT (18F-fluorocholine PET/CT) in biochemical recurrence of prostate cancer (n=205). The primary endpoint was the detection rate (DR): number of patients defined as positive at patient level by the independent readers among the total number of patients assessed (for 18F-DCFPyL and 18F-FCH PET/CT).

For initial staging (Osprey study, cohort A), the assessment of efficacy was based on evaluating technical performance (inter- and intra- reader variability), diagnostic performance, assessed by two co-primary endpoints (specificity and sensitivity), PPV, NPV, and impact on patient management.

The standard of truth (SoT) for Osprey study was histopathology, which is universally accepted. This study was divided in cohort A for initial staging (mainly N-staging) and cohort B for recurrent or metastatic PCa. Cohort B of Osprey study (n=117) is not considered as pivotal, only supportive for both indications, as the population is different from the clinical settings where efficacy is claimed.

Condor and Python studies were designed for assessing the diagnostic performance of 18F-DCFPyL PET/CT in **biochemical recurrence (BCR)** after curative therapy. A composite standard of reference (SoR) was established based on, by order of preference, histopathology or findings on conventional imaging or clinical follow-up, i.e., PSA response to RT. Using histopathology in BCR is very challenging and not always feasible in this population. Thus, a composite standard of reference may be acceptable. In Condor study the assessment of efficacy was based on evaluating technical performance (inter- and intra- reader variability), diagnostic performance (correct localisation rate at patient level, detection rates and PPV by anatomic region and baseline PSA) and change in intended management. Specificity was not calculated at patient level as all patients with recurrence based on sPSA increasing were considered positive. These efficacy endpoints are acceptable and aligned with clinical practice and the requirements of relevant guideline.

In Python study, efficacy assessment of 18F-DCFPyL PET/CT was based on comparing detection rate (DR) as primary endpoint and concordance as secondary endpoint in comparison with 18F-FCH PET/CT. Sensitivity and impact on change in intended management were also evaluated as secondary endpoints. Likewise in Condor study, specificity at patient level was not calculated as all patients with first biochemical recurrence after definitive therapy were considered as diseased. Detection rate as primary endpoint can be acceptable when confirmation with a standard of reference is feasible. In this study, only 37 patients were assessed with a standard of reference, therefore, results have limited value.

<u>Primary staging of PCa</u>: Diagnostic performance, inter- and intra-reader variablity, and impact on patient management

The population included in the cohort A of Osprey study were patients at high risk (or very high risk) as defined by NCCN guidelines version 3.2016. The main goal of initial staging in this population was the detection of metastases in lymph nodes (N-staging). Detecting distal organs metastases (M-staging) was not the objective in cohort A. Although in 12.3% of patients distant metastasis were detected and only 1 patient with osseous metastasis (M1) was confirmed by biopsy, it is recognised there is a lack of data on distant metastases and M-staging. Given that Cohort A of Osprey study was focused on N staging and that distant metastases has not been studied, relevant statement was added to the PI indicating that piflufolastat (18F) was not studied for detection of distant metastases in primary staging.

As lymph node metastases in other lymph node basins including the thorax may be present at the diagnosis, as well as bone metastasis, the applicant was requested to provide diagnostic performance data for the whole body. However, data for other locations different than pelvic lymph nodes were not analysed due to the absence of standard of reference.

Co-primary endpoint for specificity was reached (96-99%; 95%CI: 93.6-99.4) but the study is considered a failed study as the co-primary endpoint for sensitivity (31-42%; 95%CI: 19.2-54.2) did not met the pre-specified threshold of the 95%CIs >40% for at least two readers. The reason argued by the applicant was that 44% of the population in Cohort A with pathologic nodes had a maximum metastatic foci <5mm, which is under the PET scanner detection limit (Crippa et al., 2000). Therefore, a post-hoc sensitivity analysis was performed excluding these patients, and sensitivity met the success criteria whereby the lower limit of the 95%CI exceeded 40% for the same two readers. In this regard, a warning has been included in the SmPC to inform that small lymph nodes metastases, or any lesion under spatial resolution of PET (= 5 mm) may be missed by piflufolastat (18F) PET/CT (see SmPC section 4.4).

Additionally, the applicant performed a post-hoc pelvic lymph node colocalisation analysis to match true positive lesions with positive 18F-DCFPyL PET/CT results in defined templates after PLND. In this analysis, specificity was unchanged but sensitivity across all three readers was even lower (27%-37%).

The cohort A of Osprey study was not designed to obtain comparative data on diagnostic performance of 18F-DCFPyL PET/CT with other imaging modalities as requested by the guideline on clinical evaluation (Doc. Ref. CPMP/EWP/1119/98/Rev. 1) for new diagnostic agents. However, the applicant carried out a post-hoc analysis comparing the diagnostic performance of 18F-DCFPyL PET /CT with baseline conventional imaging (CT, MRI). In the post-hoc analysis comparing 18F-DCFPyL PET/CT with conventional imaging, results confirmed that sensitivity for 18F-DCFPyL PET/CT was slightly lower than conventional imaging (40.3% vs 42.6%) but specificity (97.9% vs 65.1%), PPV (86.7% vs 28.3%) and NPV (83.2% vs 77.8) was better for 18F-DCFPyL PET/CT versus conventional imaging. Higher sensitivity versus specificity in a diagnostic agent is preferred when curative therapy is feasible. In this clinical context, lower sensitivity is not so crucial, as all patients would undergo radical prostatectomy with pelvic lymph node dissection. Moreover, higher values of specificity and NPV provides higher probability to correctly classify negative results, but due to the low sensitivity, a negative result on 18F-DCFPyL PET/CT did not rule out the disease and additional diagnostic modalities are required. Corresponding warning has been included in the SmPC: Clinical correlation, which may include histopathological evaluation of the suspected prostate cancer site, is recommended. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer.

In this context, the place of 18F-DCFPyL PET/CT for initial staging in the diagnostic work-up should be in accordance with the EAU/EANM/ESTRO/ESUR/ISUP/SIOG guideline on Prostate Cancer 2022 (Mottet et al., 2022).

Comparative data about radiation exposure between 18F-DCFPyL PET/CT and CT or bone scan have been provided by the applicant (data not shown). Mean effective dose for piflufolastat (18F) PET/CT is 9 mSv versus about 15 mSv when contrast-enhanced CT + whole-body bone scan/whole-body PET/CT are used.

Additionally, the applicant has submitted evidence from the literature. In this regard, the most outstanding study is the Jansen et al., 2021 study that included 117 patients to assess the accuracy of N-staging, and 116/117 patients (99.1% with PSMA expression in the prostate at PET/CT) for the accuracy of T-staging. The Jansen et al., 2021 study was comparable in methodology and results to the Cohort A of Osprey study. Both studies are also comparable with the van Kalmthout et al., 2020 study which was selected as primary proof of efficacy for gozetotide for primary staging.

Considering that cohort A of Osprey study was a failed study for sensitivity and did not improve the sensitivity of conventional imaging for detecting N-metastases, staging was practically limited to the regional LN detection and evidence from literature is limited, the applicant has discussed the consistency of the diagnostic performance across clinical studies and literature (Cohort A vs. Jansen et al., 2021 study), showing similar data. The applicant has also discussed the place of 18F-DCFPyL PET/CT in the diagnostic work-up for initial staging.

The initial claimed indication for primary staging was "*initial staging of prostate cancer in patients at risk of metastases who are candidates for definitive therapy*". Subsequently, the applicant proposed to delete the reference to "initial staging" which was not considered adequate as only detection of PSMA positive lesions was considered vague and did not reflect accurately the use of 18F-DCFPyL PET/CT for this clinical setting.

The applicant agreed to retain primary staging in the first indication wording and submitted additional data for M-staging evidence from 40 subjects excluded from the evaluable set where 14 patients had an actual change in management due to the results on 18F-DCFPyL PET/CT (data not shown). These data on M staging cannot be accepted as supportive evidence as these subjects were excluded from the evaluable set and there are uncertainties on its validity.

Moreover, the applicant discussed the similarities between radiopharmaceuticals based on PSMA according to relevant guidelines (Mottet et al., 2023; Fendler et al., 2023; Ceci et al., 2021) and the Appropriate Use Criteria for Prostate-Specific Membrane Antigen PET Imaging (Jadvar et al., 2022).

Overall, the CHMP considered that there is enough evidence to support the wording of the first indication: "Primary staging of patients with high-risk PCa prior to initial curative therapy" given that to some extent (since expression of PSMA changes over the course of the disease) the ability of 18F-DCFPyL PET/CT to detect distant metastases can be extrapolated from the biochemical recurrence (BCR) to primary staging setting and that N-metastases can be detected with low sensitivity, but improved specificity.

Inter- and intra-reader variability was considered acceptable.

Change in intended management was evaluated using medical management questionnaires before and after 18F-DCFPyL PET/CT considering baseline clinical information of individual patient and conventional imaging data. Data showed that 18F-DCFPyL PET/CT led a change in management in 43.6% (115/264) of patients, suggesting substantial impact that 18F-DCFPyL PET has in the staging of patients with high risk prostate cancer and the downstream impact on treatment planning. 18F-DCFPyL

PET/CT results before starting the treatment could modify treatment strategy in this clinical setting but change of management based on new imaging modalities without knowing the outputs of treatment is not recommended by clinical guidelines (Mottet et al., 2022). In this regard, a warning in section 4.4 about that no clinical outcome data are currently available has been added: To date no outcome data exist to support subsequent management of patients based on PSMA-PET in the primary staging. Therefore, treatment should not be changed based on piflufolastat (^{18}F) PET/CT findings only.

Metastatic or Recurrent PCa: Cohort B Osprey study

As before mentioned, cohort B of Osprey study cannot be regarded as pivotal as population included either metastatic or presumptive recurrent patients based on findings in conventional imaging modalities amenable for histopathology confirmation. However, data from this cohort B may be considered as supportive for distal staging, both in initial staging and re-staging.

The strength of this sub-study was the use of histopathology as standard of truth for patients with radiologic findings. The main limitation is the heterogeneity of the population as including patients with radiologic evidence of local recurrence or new or progressive metastatic disease on anatomical or functional imaging modalities.

Although population in cohort B was different from cohort A, 18F-DCFPyL PET/CT demonstrated high sensitivity (93%-99%) and PPV (81%-88%) for detecting PCa within biopsied lesions in lymph nodes and in distal metastases (M-staging), but no biopsies for prostatic lesions were evaluated in cohort B. Evidence on efficacy of 18F-DCFPyL PET/CT to detect regional and distant metastases can be concluded but local metastases (T-staging) were not evaluated in overall Osprey study.

The false positive (FP) cases detected in Osprey cohort B were bone and lymph node lesions. False positive bone lesions were related to benign bone disease such as fractures and Paget's disease. PSMA expression has been observed in ganglia and 18F-DCFPyL uptake can be confounded with pathologic lymph nodes. Additionally, other malignancies, diseases and physiological uptake of 18F-DCFPyL has been reported (Ceci et al., 2021). The applicant has translated these pitfalls in the 18F-DCFPyL PET/CT interpretation into the product information (section 4.4): piflufolastat (^{18}F) accumulates in normal tissue where the density of PSMA is high including the lacrimal glands, salivary glands, liver, spleen, and kidneys. Normal organs demonstrate significant variability in the uptake of piflufolastat (^{18}F); however, the impact of tumor burden on normal uptake is minimal and unlikely to be clinically significant. The expression of PSMA can predominantly be found in prostate cancer, but can also be observed in other neoplasms (e.g. renal cell carcinoma, hepatocarcinoma, breast cancer, lung cancer and other malignancies) or non-malignant conditions (e.g hemangioma, ganglia, since they can mimic lymph nodes, benign bone disease as Paget's disease, or pulmonary sarcoidosis/granulomatosis).

Inter- and intra-reader variability was also evaluated in Osprey cohort B study with acceptable values.

In conclusion, benefit of 18F-DCFPyL PET/CT in this population may be less noticeable as patients had previous radiological evidence of metastatic or recurrent disease.

BCR: Diagnostic performance, impact on patient management and inter- intra- reader variability.

Results from clinical studies and additional evidence from literature have been submitted by the applicant to support the indication for localisation of recurrence in case of rising serum PSA levels after treatment.

In **Condor study**, diagnostic performance in patients with suspected recurrence of PCa with negative or equivocal findings in conventional imaging was evaluated. According to the applicant, it was not

feasible to calculate the specificity and NPV by patient to define the diagnostic performance of 18F-DCFPyL PET/CT due to the lack of true negative results, as all patients suffered from recurrence and were considered positive. It is agreed that calculation of specificity and NPV at patient and region level was not feasible as only positive PET lesions were followed. Furthermore, it is agreed that histopathology by biopsy was difficult to obtain, as patients included in the study had no evidence of radiologic recurrence. Diagnostic performance was assessed by correct localisation rates (CLR) as primary endpoint, which is considered a PPV at patient level where positive 18F-DCFPyL PET/CT uptake was matched with positive lesions defined by a composite standard of reference. This primary endpoint is considered adequate, as the main objective is the localisation of recurrence sites to guide treatment decision.

The composite standard of reference based on, by order of preference, histopathology or findings on conventional imaging or clinical follow-up, i.e., PSA response to RT can be considered acceptable. The SoR consisted of only 31 patients with histopathology confirmation, 100 patients with correlative imaging data and only 1 patient with PSA response after radiotherapy (RT).

This study was a positive study because the lower bound of the 95%CI (77.8-93.6) exceeded the pre-specified threshold of 20% for at least two of the three independent blinded central readers. However, some concerns were raised about the SoR and the methodology followed in this study. Firstly, only positive 18F-DCFPyL PET/CT patients were followed for efficacy evaluation which isa limitation as negative results were not studied. Secondly, local evaluation of PET images instead of central reading was used to determine the SoR, therefore, lesions that were not identified by the local readers often could not be evaluated. For correlative imaging, the criteria for determining that a lesion represented prostate cancer were largely subjective. In addition, the time for collection of follow-up imaging was only 60 days, limiting the use of change in size and shape of lesions to assess disease. These issues, particularly the subjective reference standard imaging interpretation raised the possibility of bias. Despite these limitations, diagnostic performance data are considered sufficient to support the use of 18F-DCFPyL PET/CT in PCa patients with suspected biochemical recurrence.

Furthermore, the applicant performed CLR post-analyses by standard of truth method, baseline imaging modality and prior therapy. Multiple imputation and tipping point analyses were also carried in patients with unevaluable SoR. All these analyses showed a consistently high CLR.

The impact on patient management was assessed through pre- and post- intended clinical management questionnaires. The methodology is considered acceptable. According to the clinical guidelines for PCa, localisation of recurrence in BCR after curative treatment by targeted radiopharmaceuticals is recommended when change in patient management is expected. In this study, the impact of 18F-DCFPyL PET/CT on patient management was an important secondary endpoint. Results shed a positive impact on change in intended management after 18F-DCFPyL PET/CT (63.9%; 95%CI: 56.9-70.5).

Diagnostic performance of 18F-DCFPyL PET/CT in BCR was affected by PSA levels. The applicant analysed the CLR and detection rate (DR) by baseline PSA levels. As expected, detection rate increased with higher baseline PSA levels. These results have a relevant impact on the diagnostic performance for biochemical recurrence, and results have been included in the product information (see SmPC section 5.1).

Detection rate and PPV was also calculated by anatomic region level (prostatic, pelvic and extrapelvic region), showing a high PPV in all anatomic regions and lower DR in prostate region (17.8-21.2) compared with pelvic region (33.7-37.5) and extra-pelvic region (25.5-3.3).

Inter- and intra-reader variability evaluation was performed and was acceptable.

No direct comparison with other authorized radiopharmaceuticals for BCR (Axumin (fluciclovine (18F)) or 18F-FCH) was performed in the Condor Study. However, the applicant carried over the Python study, a prospective, multicenter and comparative study performed in European countries to demonstrate superiority of 18F-DCFPyL PET/CT versus 18F-FCH PET/CT.

In **Python study**, a cross over comparison between the investigational medicinal product and an acceptable comparator (18F-FCH) approved for localisation of BCR after definitive therapy was performed as required by the guideline on diagnostic agents. Patients with confirmed histopathology of prostate adenocarcinoma at first BCR after definitive therapy were included in this study, independently of results in baseline conventional imaging modalities.

Detection rate (DR) was the primary endpoint to assess diagnostic performance. This can be acceptable, as sensitivity and specificity are difficult to calculate due to the difficulty to obtain histological confirmation in this clinical setting. However, only comparing detection rate without confirmation with a robust SoR is considered not sufficient to demonstrate efficacy as required by the relevant guideline for evaluation of diagnostic agents. Only comparison of detection rates from both radiopharmaceuticals has limited value as these radiopharmaceuticals have different diagnostic performance, mechanism of action, biodistribution and different physiological uptake. These issues raised uncertainties on the results. These shortcomings could have been overcome with an acceptable standard of reference to confirm the localisation of recurrence with both radiopharmaceuticals. Notwithstanding, some efficacy data have demonstrated superiority of 18F-DCFPyL PET/CT versus 18F-FCH PET/CT on overall DR and on DR by subgroups considering initial treatment, PSA levels, PSAdt, D´Amico risk class and ISUP grade.

The study was a positive study because the differences on DR at patient level between 18F-DCFPyL PET/CT and 18F-FCH PET/CT were significative (P-value <0.0001) and the 12% increase on DR at patient level was reached (58.2% vs 40.3%) respectively. However, results on DR for 18F-DCFPyL PET/CT and 18F-FCH PET/CT were lower than reported in literature. The drastic conditions used in a controlled clinical study may have influenced the performances compared to literature reports.

18F-DCFPyL did not seem to perform better than 18F-FCH in disease detection in the pelvic and ePLNs. However, when discordant cases were analysed by the truth panel, correct localisation rate results of 18F-DCFPyL PET/CT in pelvic LN and extra-pelvic LN were better than correct localisation rate with 18F-FCH PET/CT.

Sensitivity was a secondary objective. The Truth Panel assessed only 37 patients per region according to the SoR. The SoR consisted of the combination of test available at baseline and performed in clinical routine practice up 10 months after last radiopharmaceutical injection. This follow-up was at discretion of the investigator. No data about the criteria followed to classify each case is provided. Neither justification of follow-up time, nor findings if histopathology was used, i.e., location, number and size of lesion, metastatic pattern (oligo- multi-metastatic). However, the criteria followed was based on routine practice during multidisciplinary meetings taking into account the baseline information, histopathological conclusions, and additional imaging examinations if performed during the follow-up. This can be considered adequate as it reflects the current clinical practice.

Detection rate intra- and inter- variability was calculated at patient level but some discrepancies in intra- reading for 18F-DCFPyL PET/CT were shown but no with 18F-FCH PET/CT. Inter-reader agreement was moderate, Fleiss' kappa 0.55 (0.47; 0.63) and 0.54 (0.45; 0.63). Images should be interpreted only by readers trained in the interpretation of PET images with piflufolastat (18F). In this regard, an updated RMP to include a reader training as additional risk minimization measure has been proposed by the applicant. This is considered adequate.

Concordance rate at region level was evaluated in Python study, showing acceptable results between 18F-DCFPyL PET/CT and 18F-FCH PET/CT. Discordant results were analysed by the Truth panel using the SoR.

The impact on patient management was also assessed by the Truth Panel in two ways, prospectively as proposed by the Truth panel resulting 26.0% (n=53/204) for 18F-DCFPyL PET/CT and 21.3% (n=43/202) for 18F-FCH PET/CT. The second way was after implementing treatment considering PET information. The Truth Panel determined retrospectively the impact resulting 44.1% for 18F-DCFPyL PET/CT versus an impact of 28.7 for 18F-FCH PET/CT. Methodology and results are considered acceptable.

In conclusion, Python study can be considered as supportive for localisation of biochemical recurrence after curative therapy. Considering the evidence presented with the most robust Condor study, the additional supportive data from Cohort B of Osprey study and the literature submitted by the applicant, overall clinical benefit is considered shown for this indication.

The wording of the indication for localisation of recurrence in case of rising serum PSA levels has been adapted according to the data submitted and focused on the type of recurrence and definitive therapy patients were undergone (see SmPC section 4.1). The applicant has also presented sufficient data on 18F-DCFPyL PET/CT from literature to support efficacy for localisation of recurrence in BCR setting.

2.6.7. Conclusions on the clinical efficacy

Data submitted by the applicant are considered sufficient to substantiate the claimed indications for Primary staging of patients with high-risk PCa prior to initial curative therapy and to localize recurrence of PCa in patients with a suspected recurrence based on increasing serum prostate-specific antigen (PSA) levels after primary treatment with curative intent.

From the submitted data it can be concluded that Pylclari PET/CT may contribute to the diagnostics of PCa during primary staging and localisation of recurrence in case of rising serum PSA levels after treatment.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The overall safety profile is based on data from its administration to 797 patients from three clinical studies OSPREY, CONDOR and PYTHON and spontaneous reporting.

Safety analyses were performed on the following populations:

- Pooled Safety Population from OSPREY and CONDOR (n=593).
- Recurrent or metastatic PCa Analysis Group (n=325). A subset of pooled safety population including only patients from OSPREY Cohort B and CONDOR, and based on their similar characteristics (men with recurrent or metastatic PCa).
- High Risk PCa Analysis Group (n=268): A subset of pooled safety population including only patients from OSPREY Cohort A.

- Safety Population from PYTHON (n=204). Patients with first BCR who received a dose of 18F-DCFPyL in PYTHON.
- Urinalysis Set (OSPREY): Patients who received a dose of 18F-DCFPyL and have urinalysis results in an investigator-sponsored trial.

All patients received a single IV injection. Patients from OSPREY and CONDOR received 333±37 MBq as a single IV injection, PET/CT initiated 60-120 minutes after injection and patients from PYTHON were planned to receive one single intravenous injection of 330 MBq of 18F-DCFPyL (330-360 MBq) and one single intravenous injection of 18F-FCH at an activity of 2 to 4 MBq/kg body weight (140-280 MBq). The order or administration was randomized. A 10 % variation in target activity was allowed. PET/CT initiated 120 (± 15) minutes after injection.

2.6.8.2. Adverse events

In OSPREY, TEAEs were defined for all patients as AEs occurring from the day of, but after 18F-DCFPyL administration, through the date of (but prior to) surgery or through 21 (± 7) days post-biopsy.

In CONDOR, AEs were captured from the time of administration until the scheduled safety follow-up telephone call 7 (±3) days after dosing.

In both study populations, 65 patients (11%) had TEAEs. Majority had Grade 1 (mild) TEAEs (51, 9%) than Grade 2 (moderate) (8, 1%) or Grade 3 (severe) (6, 1%). No patient had a Grade 4 (life threatening) or Grade 5 (fatal) TEAE.

A larger proportion of patients with at least one TEAE was reported in the high-risk group (39, 15%) compared to the recurrent or metastatic group (26, 8%).

However, most patients in the high-risk group (37/39, 95%) had only Grade 1 TEAEs.

Out of all the TEAEs, 5% (30 patients) were drug related. Most common TEAEs reported in less than 1% of the population. These were headache (2%), dysgeusia (2%) and fatigue (1%) and these usually showed up between day 1 and day 3 drug dosing.

In PYTHON, TEAEs were considered when appeared at the time or during the following 24h after drug administration. Four patients reported at least one TEAEs, and a total of 6 types of TEAEs were observed, the most common (which occurred in ≥1% of patients) were headache. None led to discontinuation of treatment.

Among the 797 patients, a total of 108 treatment emergent adverse events (TEAEs) were reported in 69 (8.6 %) patients, with headache (1.4%), dysgeusia (1.0%), and fatigue (0.5%) being the most frequent. Three serious drug-related adverse events (hypersensitivity, headache, and paresthesia) were reported, all experienced by one patient and only hypersensitivity was assessed as drug-related in this patient who had a significant history of allergic reactions. All three serious drug-related adverse events were resolved.

Table 35. Adverse reactions observed with piflufolastat (^{18}F)

MedDRA body system organ class	Adverse reactions	Frequency
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Dehydration	Uncommon
Psychiatric disorders	Disorientation	Uncommon

Nervous system disorders	Syncope	Not known*
	Dysgeusia	Common
	Headache	
	Dizziness	Uncommon
	Hyperaesthesia	
	Migraine	
Eye disorders	Visual field defect	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Gastrointestinal disorders	Nausea	Not known*
	Vomiting	
Skin and subcutaneous tissue disorders	Dry skin	Uncommon
	Rash	
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon
	Muscular weakness	
	Pain in extremity	
Renal and urinary disorders	Dysuria	Uncommon
General disorders and administration site conditions	Fatigue	Uncommon
	Chest discomfort	Uncommon
	Application site rash	
	Feeling abnormal	
	Injection site pain	

*Adverse reactions derived from spontaneous reporting with a not known frequency.

2.6.8.3. Serious adverse event/deaths/other significant events

In studied population, eight patients (1%) in the safety population had reported SAEs; seven with recurrent or metastatic PCa and one with high risk PCa. SAEs are summarized in Table 39.

Table 36. Serious Adverse Events (Pooled Safety Population of OSPREY and CONDOR)

Patient Number	System Organ Class/ Preferred Term/ Verbatim Term	Start Day/ Stop Day[1]	AE Duration in days[2]	Severity Grade[3]	Outcome/ AE Led to Study Discontinuation?	Relationship to Study Drug
High Risk PCa						
	Cardiac disorders/ Coronary artery disease/ Coronary Artery Disease	4/5	2	2	Recovered/resolved/ No	Unrelated
Recurrent or Metastatic Cancer PCa						
	Metabolism and nutrition disorders/ Hyperkalaemia/ Hyperkalaemia	2/3	2	3	Recovered/resolved/ No	Unrelated
	Cardiac disorders/ Atrial fibrillation/ Atrial fibrillation with RVR	34/36	3	2	Recovered/resolved with sequelae/ No	Unrelated
	Nervous system disorders/ Spinal cord compression/ Pain secondary to spinal cord compression	54/55	2	3	Recovered/resolved/ No	Unrelated
	Gastrointestinal disorders/ Lower gastrointestinal haemorrhage/ Lower gastrointestinal haemorrhage	22/30	9	3	Recovered/resolved with sequelae/ No	Unrelated
	Infections and infestations/ Pyelonephritis acute/ Acute pyelonephritis	34/36	3	2	Recovered/resolved/ No	Unrelated
	Cardiac disorders/ Coronary artery disease/ Coronary heart syndrome	15/16	2	3	Recovered/resolved with sequelae/ No	Unrelated
	Immune system disorders/ Hypersensitivity/ Allergic reaction	3/4	2	3	Recovered/resolved/ No	Related
	Nervous system disorders/ Headache/ Headache	7/9	3	3	Recovered/resolved/ No	Unrelated
	Nervous system disorders/ Paraesthesia/ Left arm paraesthesia	7/9	3	3	Recovered/resolved/ No	Unrelated

AE=adverse event; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PCa=prostate cancer.
[1] Start Day and Stop Day are relative to the day of dosing, defined as Day 1.
[2] AE Duration = Stop Date – Start Date + 1.
[3] Severity Grade (NCI CTCAE v4.03): 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death.

Patients number have been removed for anonymisation purposes.

Two patients reported coronary artery disease and one patient reported the other SAEs.

Two severe SAEs, hypersensitivity reaction and hyperkalaemia, were reported with a start date between days 2-3. Hypersensitivity reaction was assessed as related to study drug, and hyperkalaemia was assessed as unrelated to study drug. All mild to moderate SAEs were reported on day 4 or later.

No deaths were reported in OSPREY, CONDOR or PYTHON. No SAEs were reported and no treatment discontinuations in PYTHON.

2.6.8.4. Laboratory findings

- **Haematology and clinical chemistry**

Shifts out of the normal range were most common for normal to low haematocrit (8% of patients), erythrocytes (7%), and haemoglobin (5%) and normal to high leukocytes (85%).

For clinical chemistry lab shifts out of the normal range were most common for normal to high glucose (9% of patients), normal to low calcium (7%), normal to high bilirubin (6%), and normal to high blood urea nitrogen (4%).

According to the applicant seven patients had clinically significant abnormalities at follow-up that were not present at baseline (high alanine aminotransferase in 2 patients; high glucose, high aspartate aminotransferase, high bilirubin, high triglycerides, and high potassium in 1 patient each).

Leukocyte and Triglyceride results were not reported for the majority of patients at follow-up .

- **Vital signs**

Blood pressure and pulse rate were almost unchanged from baseline in study OSPREY and CONDOR.

For PYTHON, changes were measured 15min and 2 hours (± 15min) after injection. Neither blood pressure nor pulse rate changed.

- **Electrocardiogram**

Data were collected from 12 patients before and after drug dosage.

- **Urinalysis**

Urine samples were collected for analysis 24 hours after drug dosage and were collected for nine patients of the total of study population.

For these patients, the presence of bilirubin, blood, nitrite and protein were negative.

2.6.8.5. Safety in special populations

- **Intrinsic Factors**

Following IV administration of 18F-DCFPyL at the recommended dose of 4 MBq/Kg BW, the highest estimated radiation absorbed dose was in the kidneys. Furthermore, pharmacokinetic data showed that 18F-DCFPyL is excreted in the urine. Therefore, TEAEs were examined by renal function for patients in OSPREY. The incidence of TEAEs was 16/105 (15%) for patients with normal renal function, 28/245 (11%) for patients with mild renal impairment, and 6/30 (20%) in patients with moderate/severe renal impairment. There were no notable differences in the incidence of TEAEs by renal function.

The most common TEAEs, headache, dysgeusia, and fatigue, were reported only in patients with normal renal function or mild renal impairment.

TEAEs related to 18F-DCFPyL are summarised by age group (<65 and ≥65 years)

The incidence of the most common TEAEs was similar in each age group. Headache was reported in 6 patients (3%) <65 years old and 7 patients (2%) ≥65 years old; dysgeusia, in 6 patients (3%) and 4 patients (1%); respectively; and fatigue, in 4 patients (2%) and 3 patients (1%), respectively.

Among the 238 patients who were <65 years old, 31 (13%) had TEAEs, and of 355 patients who were ≥65 years old, 34 (10%) had TEAEs.

Safety analysis by age group has not been performed in PYTHON.

2.6.8.6. Safety related to drug-drug interactions and other interactions

See 2.6.9.

2.6.8.7. Discontinuation due to adverse events

There has been no discontinuation of 18F-DCFPyL treatment due to adverse effects.

2.6.8.8. Post marketing experience

PYLARIFY (piflufolastat F 18) Injection was approved by the US FDA on 26 May 2021 for PET of prostate-specific membrane antigen (PSMA) positive lesions in men with PCa: with suspected metastasis who are candidates for initial definitive therapy and with suspected recurrence based on elevated serum PSA level. During the period 26 May 2021 to 17 November 2022, 98 533 patients were exposed to PYLARIFY. No new safety signals have been identified from marketing experience. Till the launch on the US market, no new safety signals have been identified from marketing experience in respect of approved use, off-label use, administration to special populations, medication errors, overdose or abuse.

One single patient experienced five serious adverse reactions within a few minutes after PYLARIFY administration: syncope, nausea, vomiting, dizziness, and headache. He was transported to the emergency department, recovered from the events, and was discharged home in stable condition that same day. Syncope, nausea, and vomiting were not listed in the SmPC, and considered as related to PYLARIFY, and therefore added with a 'not known' frequency.

In Spain, compassionate use was approved for 18F-DCFPyL on June 19, 2020. From 16 July 2020 till 17 November 2022, 5625 patients received 18F-DCFPyL. Additionally, during the same period, 186 patients were exposed under name-patient basis approval in Belgium, and 1360 in the Netherlands. There have been no new safety signals identified in these programs.

2.6.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Studies OSPREY, CONDOR and PYTHON support the use of Pylclari as a radiopharmaceutical diagnostic agent for (1) the primary staging of patients with high risk PCa prior to initial curative therapy; and (2) the localisation of recurrence of PCa with a suspected recurrence based on increasing PSA levels after primary treatment with curative intent.

The safety database is composed of 797 patients, 593 for studies OSPREY and CONDOR and 204 for study PYTHON who received a single injection of 18F-DCFPyL. 268 patients had high risk PCa (OSPREY Cohort A) and 325 patients had recurrent or metastatic PCa (OSPREY Cohort B and CONDOR). The population included in the trials is the one expected for the evaluation of this class of products.

Safety data from studies OSPREY and CONDOR has been pooled for most analyses. This is reasonable as similar dose of the product was used in both trials and both studies enrolled prostate cancer patients so relevant differences between disease status are not expected to impact safety. Nevertheless, data from study PYTHON could have been included in an "integrated safety report" rather than presenting its safety results in isolation, as differences in safety in the studied population are not expected either.

Additionally, 2228 patients have received at least one dose of 18F-DCFPyL in ongoing clinical trials for which safety data are not available for assessment. A summary of safety data from 230 prostate cancer patients coming from two published clinical trials is also available. Overall, the safety database is regarded adequate.

Mean recommended activity for 18F-DCFPyL was 330 MBq (range: 300-360 MBq), administered as a single intravenously (IV) dose. The median decay corrected dose at the time of administration was 340.4 MBq in OSPREY and CONDOR, and 321.19 (186.9-373.0) MBq in PYTHON.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 4.2 mSv when the maximal recommended activity of 360 MBq is administered in a 70 kg-weighted patient, these adverse reactions are expected to occur with a low probability.

The dose administered in the trials was not adjusted by age, BMI or renal function. It seems acceptable since there were no significant differences between the BMI of the patients in the three studies, neither by renal function nor by age range. The applicant has proposed the dose by BW to be aligned with the majority of diagnostic radiopharmaceuticals which is acceptable. The mean recommended activity of (^{18}F) piflufolastat is 4 MBq/kg of body weight and can vary from 3 to 5 MBq/kg of body weight depending on the PET equipment and acquisition mode used. The minimum activity should not fall below 190 MBq and the maximum activity should not exceed 360 MBq. (see also 2.6.6 and 2.6.8.1).

Piflufolastat (^{18}F) has only been studied in patients with mild renal impairment. 18F-DCFPyL is excreted mainly by renal way. There were no data on severe renal impairment but the applicant has discussed the impact of radiation exposure in these patients, and has included appropriate information in section 4.2, 4.4 and 5.2 of SmPC.

The product currently is not intended to be used in women, and this is reflected in the PI. It is also not intended to be used in paediatric population due to specificities of the disease.

The safety profile of 18F-DCFPyL appears benign. The incidence of AEs was quite low and AEs were manageable. The most common AEs was headache. Hypersensitivity was reported in 1% of patients from the clinical trials. Anaphylactic reactions are correctly included in sections 4.4 and 4.8 of the SmPC. Overall, the adverse event profile is adequately reflected in the product information proposed.

One serious AEs was considered related to treatment (hypersensitivity). No deaths were reported.

Only one case of syncope derived from spontaneous reporting in the post-marketing use in the USA has been identified and included in the SmPC.

Clinically relevant changes in laboratory parameters were reported in seven patients in study OSPREY but overall, these findings are considered unlikely related to 18F-DCFPyL considering to low mass dose administered. Changes in mean QTc values were not clinically relevant.

Differences between regions (European versus non-European) do not seem relevant in terms of incidence of AE. The impact of other extrinsic factors has not been discussed by the applicant.

Due to the extremely low chemical mass in an administered dose, meaningful interactions with metabolising enzymes, transporters, or ion channels are highly unlikely (Pre-IND WRO, 2016). In addition, 18F-DCFPyL does not undergo meaningful metabolism, as demonstrated in PCa patients, indicating that blood concentrations of 18F-DCFPyL are not expected to be affected by the presence of concomitant inducer or inhibitor drug.

Data from published literature do not suggest additional AEs although the limitations of the interpretation of these data are fully acknowledged.

Safety data available from post-marketing experience (from the USA) and from compassionate programmes with cut-off dates of 2022 have been provided. Safety data looks consistent with what is known from the clinical trials.

Incorrect image interpretations can have important consequences for the patients therefore images should be interpreted only by readers trained in the interpretation of PET images with piflufolastat (18F). In this regard, 'PET imaging interpretation errors' is included in the RMP as an important potential risk and a reader training is to be set up as additional risk minimization measure. Moreover, an observational study to evaluate Physician Training Methods to read (18F)-DCFPyL PET scans will be performed by the applicant to address the question of the effectiveness of (18F)- DCFPYL training programme to prevent PET imaging interpretation errors (false negative investigation result, false positive investigation result). See also section 2.7.

Specifications related to radiation protection in the context of manipulation and elimination of the radiopharmaceutical by healthcare professionals, and radiation protection for the family have been adequately discussed. Close contact with infants and pregnant women should be restricted during the initial 12 hours following the injection (see SmPC section 4.4). Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation. Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken[4] (see SmPC section 6.6).

This product is administered via an intravenous flexible catheter. The administration must be strictly intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts. The bolus administration will be followed by a flush of 5-10 mL sodium chloride 9 mg/mL (0.9%) solution for injection, to ensure full delivery of the dose. Instructions on dilution of the medicinal product before administration have been included in the SmPC (see section 12). If at any time in the preparation of this medicinal product the integrity of the vial is compromised it should not be used. Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory. The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken. Any unused medicinal product or waste material should be disposed of in accordance with local requirements[5].

18F-DCFPyL could be used for the same patients more than once (for instance, for monitoring of disease progression, or treatment effects, etc). The applicant has discussed the safety of repeated injections of 18F-DCFPyL, and repetition of 18F-piflufolastat PET/CT is not considered as an issue.

[4] This is general information from the Core SmPC for radiopharmaceuticals
[5] This is general information from the Core SmPC for radiopharmaceuticals

2.6.10. Conclusions on the clinical safety

In conclusion, a single administration of Pylclari (piflufolastat (18F)) as an I.V. injection, mean 4 MBq/Kg BW from 3 to 5 MBq/kg of body weight, is considered to have an acceptable safety profile given low number of safety reports in clinical trials and in the literature and mostly mild severity of the reported AEs.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 37. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	PET imaging interpretation errors
Missing information	None

2.7.2. Pharmacovigilance plan

2.7.2.1. Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted.

2.7.2.2. Summary of additional PhV activities

Table 38. On-going and planned additional pharmacovigilance activities

Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Observational study to evaluate Physician Training Methods to Read (18F)-DCFPyLPET Scans (Planned)	Primary endpoint: Evaluate the efficacy of the educational material Secondary endpoint: Evaluate the impact of demographic and other factors (such as years of experience of the reader, method of training, gap between training and reading, and country) on diagnostic accuracy to try to identify factors that may be associated with image interpretation errors.	Effectiveness of (18F)- DCFPYL training programme to prevent PET imaging interpretation errors (False negative investigation result, False positive investigation result)	Submission of study protocol	Q1 2024

2.7.2.3. Overall conclusions on the PhV Plan

Having considered the data submitted, the proposed post-authorisation PhV development plan is considered sufficient to identify and characterise the risks of the product and the post-authorisation development plan is sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3. Risk minimisation measures

- ***Routine Risk Minimisation Measures***

There are no routine risk minimisation measures beyond the product information.

- ***Summary of additional risk minimisation measures***

Table 39. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
- PET imaging interpretation errors (false negative and false positive)	SmPC sections 4.2, 4.4 and 5.1 Additional risk minimisation measures: Healthcare Professional self-training material Educational materials of nuclear physicians qualified to interpret (18F)-DCFPYL PET scans	PASS - To assess the effectiveness of the educational materials (Healthcare Professional self-training material).

Additional risk minimisation measures are in line with other similar approved products and are considered acceptable.

- ***Overall conclusions on risk minimisation measures***

Additional risk minimisation measures include a self-training program aimed to reduce the potential risk of PET imaging interpretation error.

The proposed risk minimisation measures are considered sufficient to minimise the risks of the product in the proposed indication.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 26.05.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the '*Guideline on the readability of the label and package leaflet of medicinal products for human use'.* Indeed, the user consultation complies with the requirements and recommendations of articles 59(3) and 61(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC. This package leaflet was found to contain all the necessary information in a way that is accessible and understandable to those who participated in this test.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Pylclari (piflufolastat (18F)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indications are 1) initial staging of prostate cancer in patients at risk of metastases who are candidates for definitive therapy, and 2) for localisation of recurrence in case of rising serum PSA levels after treatment.

Prostate cancer is a significant cause of morbidity and mortality in EU: according to data from Eurostat, about 65 200 men died from PCa in 2016. The standardised death rate from prostate cancer stood in EU at 38 deaths per 100 000 male inhabitants. Early identification of metastatic disease, both at initial staging and at any point after initial definitive therapy may have the potential to improve patient outcomes. Indeed, up to one half of men treated with curative intent following a diagnosis of primary PCa will experience the recurrent disease within 10 to 15 years following therapy. The use of a non-invasive whole-body functional imaging to reliably detect, monitor, and restage PCa will offer physicians valuable information on a patient's disease state and improve treatment management.

Diagnostic work-up of PCa is complex. Main task of staging is identification of extent of the primary tumour (T), lymph node (N) involvement, and presence or absence of distant metastases (M), along with the serum prostate-specific antigen (PSA) level and the histologic grade group (based on the Gleason score) of the primary tumour to classify men into prognostic stage groups to further decide on optimal treatment strategy. Various diagnostic imaging tools (CT, MRI, PET, bone scan, etc.) are applied to support PCa diagnosis (primary and after definitive therapy and return of PSA elevation) and

primary staging/restaging. Conventional imaging modalities (e.g., CT, MRI, whole body bone scintigraphy) are suboptimal for detecting small metastatic lesions or occult locoregional recurrence.

3.1.2. Available therapies and unmet medical need

The EAU-EANM-ESTRO-ESUR-ISUP–SIOG Guidelines on prostate cancer (Mottet el al., 2022) recommends that for initial staging, the patients with high-risk disease are staged for metastases using at least cross-sectional abdominopelvic imaging and a bone-scan. According to this guideline, evidence shows that choline PET/CT, PSMA PET/CT and whole-body MRI provide a more sensitive detection of LN- and bone metastases than the classical work-up with bone scan and abdominopelvic CT. Replacing bone scan and abdominopelvic CT by more sensitive imaging modalities may be a consideration in patients with high-risk PCa undergoing initial staging. However, the guideline remarks that in absence of prospective studies demonstrating survival benefit, caution must be used when taking therapeutic decisions.

In patients suffering BCR after curative treatment, PSMA-PET/CT is recommended only if the results may influence subsequent therapy. According to the above guideline, in patients with BCR, imaging can detect both local recurrences and distant metastases, however, the sensitivity of detection depends on the PSA level. After radical prostatectomy (RP), PSMA PET/CT seems to be the imaging modality with the highest sensitivity at low PSA levels (<0.5 ng/mL) and may help distinguishing patients with recurrences confined to the prostatic fossa from those with distant metastases which may impact the design and use of post-RP salvage radiotherapy (RT). After RT, MRI has shown excellent results at detecting local recurrences and guiding prostate biopsy. Given the substantial morbidity of post-RT local salvage treatments, distant metastases must be ruled out in patients with local recurrences and who are fit for these salvage therapies. Choline-, 18F-fluciclovine- or PSMA-PET/CT can be used to detect metastases in these patients but for this indication PSMA PET/CT seems the most sensitive technique.

Overall, it is recognised that conventional imaging modalities display lower sensitivity in prostate cancer diagnostic than PET/CT with 18F-fluciclovine, Choline- and PSMA based radiopharmaceuticals. Moreover, better sensitivity for PSMA PET/CT has been reported over radiopharmaceuticals based on choline and 18F-fluciclovine.

Recently, gozetotide (PSMA-11) under the trade name Locametz was approved in the EU as a kit for radiopharmaceutical preparation (EMEA/H/C/005488). Additionally, the radiopharmaceutical ready for use, 18F-PSMA-1007, under the trade name of Radelumin has been approved in some EU countries (FR/H/0797/001-002MR) in the same clinical settings than Pylclari (PET performance in patient with BCR of PCa after RT).

Considering the increasing use of PSMA PET/CT in the EU and the above clinical practice recommendations for these clinical settings, the approval of a new PSMA based radiopharmaceutical is expected to be of benefit in the diagnostic of PCa across the European Union countries.

3.1.3. Main clinical studies

Main clinical studies are summarised as follows:

Primary staging

Osprey study, cohort A (n=268): A multicentre, phase 2/3, open-label, nonrandomised, controlled study designed to assess the diagnostic performance of 18F-DCFPyL PET/CT against histopathology, focused on lymph nodes assessment after dissection (N staging), in patients at high risk of PCa planned to undergo radical prostatectomy (RP) with pelvic lymph node dissection (PLND). Co-primary endpoints were specificity and sensitivity of piflufolastat (18F) PET/CT against histopathology within the pelvic lymph nodes.

The Osprey study, cohort B (n=117), was designed to assess the diagnostic performance of 18F-DCFPyL PET/CT in patients with metastatic or recurrent PCa with radiologic evidence of disease. This cohort may be considered as supportive of the two claimed indications as population is not represented in the clinical settings where efficacy is claimed.

BCR

- Condor study (n=208): A multicentre, phase 3, open-label, single-arm, nonrandomised, controlled study aimed to determine the correct localisation rate (CLR) of 18F-DCFPyL PET/CT in the detection of recurrent PCa at the patient level in patients suffering from BCR after definitive therapy and with negative or equivocal baseline imaging information. Lesions were validated by a composite reference standard (histopathology or correlative imaging or clinical follow-up, by order of preference).

- Python study (n=215): a multicentre, phase 3, open-label, cross-over, randomised, controlled study aimed to compare per-patient detection rate of 18F-DCFPyL PET/CT versus 18F-FCH PET/CT (superiority) in patients at first BCR after definitive therapy. Lesions were validated by a composite reference standard (histopathology or correlative imaging or clinical follow-up, by order of preference).

3.2. Favourable effects

Primary staging

Cohort A Osprey study Initial staging

Diagnostic performance:

PLNs (N stage): Specificity: 96.3-98.9%, Sensitivity: 31-42%, PPV: 75-89.5%, NPV: 91.3-93.5%

Relative to the diagnostic performance of conventional imaging (post-hoc analysis), sensitivity was comparable, NPV was slightly higher, specificity was improved, and PPV of 18F-DCFPyL PET was 3-fold higher with 18F-DCFPyL PET, notably due to lower FP rate.

Change in intended initial therapy planning: 44% of patients.

Cohort B Osprey study: Recurrent or metastatic PC

Diagnostic performance:

Sensitivity 92.9-98.6% and PPV 81.2-87.8%

BCR

Condor study

Diagnostic performance

Correct localisation rate (CLR), patient-level: 84.8-87.0%.

-Prostatic region: Detection rate 18-21%; PPV 75-83%

-Pelvic region: Detection rate 34-38%; PPV 67-73%

-Extra-pelvic region: Detection rate 26-31%; PPV 67-70%

-In patients with PSA <2.0 ng/mL (n=139), CLR ranged from 77-78%

Change in intended management: 64% of patients.

Python study

Diagnostic performance:

Detection rate (DR): 58.2% versus 40.3% compared with 18F-FCH (P<0.0001)

Change in intended management: 41% versus 29% compared with 18F-FCH.

3.3. Uncertainties and limitations about favourable effects

Pylclari is dosed based on body weight. Supportive evidence (dose-finding studies) for this body weight based dosing was not provided. However, a further analysis was made across all 3 pivotal studies (PYTHON, OSPREY, CONDOR) showing that the mean injected activity per kilogram of body weight and the median activity were quite homogeneous across the 3 studies: mean activity of 3.87 MBq/kg. Therefore, the mean recommended activity of (18F) piflufolastat is 4 MBq/kg of body weight and can vary from 3 to 5 MBq/kg of body weight depending on the PET equipment and acquisition mode used. The minimum activity should not fall below 190 MBq and the maximum activity should not exceed 360 MBq.

- *Initial staging indication: initial staging of prostate cancer in patients at risk of metastases who are candidates for definitive therapy*.

The cohort A in Osprey study was a failed study, as sensitivity did not reach the prespecified threshold. However, specificity, PPV and NPV were better for 18F-DCFPyL PET/CT than conventional imaging. Higher sensitivity versus specificity in a diagnostic agent is preferred when curative therapy is feasible. In patients who are candidates for definitive therapy, lower sensitivity is not so crucial, as all patients would undergo radical prostatectomy with pelvic lymph node dissection, and higher values of specificity and NPV provide higher probability to classify correctly negative results, which is a benefit for patients. However, due to the low sensitivity, a negative result on 18F-DCFPyL PET/CT does not rule out the disease, and additional diagnostic modalities are required. To address this uncertainty, a warning has been added in the SmPC: Clinical correlation, which may include histopathological evaluation of the suspected prostate cancer site, is recommended. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer.

The selected population in Cohort A consisted of PCa patients at high risk of metastases and the first indication adequately reflects the risk categorization of the population. However, the Cohort A was focused mainly on regional metastases detection (N staging), while no evidence was provided on local staging (T staging). Additional evidence for the whole body (Cohort B of Osprey study) and for T-staging from literature (Jansen et al. 2021) was provided as supportive information. The CHMP considered that there is sufficient evidence to support the use of Pylclari for primary staging of

patients with high-risk PCa prior to initial curative therapy given that to some extent (since expression of PSMA changes over the course of the disease) the ability of 18F-DCFPyL PET/CT to detect distant metastases can be extrapolated from the biochemical recurrence (BCR) to primary staging setting and that N-metastases can be detected with low sensitivity, but improved specificity.

The limitations of the submitted evidence (lack of data on distant metastases and M-staging, that co-primary endpoint on sensitivity failed, that PET did not improve sensitivity compared to conventional imaging) have been adequately reflected in the product information.

- Condor study

Some concerns have been raised related to the composite standard of reference (SoR) that could have biased the results.

Local evaluation of PET images instead of central reading was used to determine the SoR. The applicant clarified that, without a truth standard, the patient was considered unevaluable for the primary analysis. The primary endpoint of correct localization rate for the 3 central readers with the respective 95% confidence intervals were: Reader 1: 85.6% (78.8, 92.3); Reader 2: 87.0% (80.4, 93.6), Reader 3: 84.8% (77.8, 91.9). A sensitivity analysis was performed treating all unevaluable patients as false positive scans. The results (Table 10 of CSR) were: 80.2% (95% CI: 72.8%-87.6%), 82.1% (95% CI: 74.8%-89.4%), and 80.8% (95% CI: 73.2%-88.3%) for Readers 1-3, respectively.

The SoR consisted of only 31 patients with histopathology confirmation, 100 patients with correlative imaging data and only 1 patient with PSA response after radiotherapy (RT). Correlative imaging criteria were subjective but considered acceptable as although subjective, the criteria for determining a lesion as positive or negative was predefined in the section 8.3 of the imaging review charter.

The time for collection of follow-up imaging was only 60 days, limiting the use of change in size and shape in lesions to assess the disease. The protocol was designed to have the truth standard obtained within 60 days of the PET scan so that the two assessments could be obtained within a short period before disease progression could potentially occur. This relatively short interval was intended to reduce potential bias that could occur in case of a longer time interval between the PET scan and the assessment of standard of truth. The time for collection of follow-up was predefined in the imaging review charter of Condor study.

- Python study

The validity of the study is a concern due to the deficiencies in the composite standard of reference.

Only 37 patients were assessed per region. This is due to few patients undergoing other imaging tests, making impossible to determine the SoR in most of the patients, and that the majority, especially in case of one positive PET/CT, received subsequent systemic therapy, which made it impossible to determine the SoR at a region level.

SoR consisted of the combination of test available at baseline and performed in clinical routine practice up 10 months after last radiopharmaceutical injection. This follow-up was at discretion of the investigator. No data are provided about the criteria followed to classify each case according to the standard of reference. According to the applicant, the criteria followed was based on routine practice during multidisciplinary meetings taking into account the baseline information, histopathological conclusions, and additional imaging examinations if performed during the follow-up. This can be considered adequate as it reflects the current clinical practice.

3.4. Unfavourable effects

Around 11% of patients participating in the clinical development had AEs. The most common was headache (1.2% for recurrent or metastatic PCa, 1% in PYTHON study), and dysgeusia (3.4%) for patients in the high-risk group of PCa in the pooled analysis, and none for the PYTHON study. Hypersensitivity was reported by 1% of patients in the pooled analysis and by none in the study PYTHON.

SAE were reported in 10 patients in studies OSPREY and CONDOR although all except the hypersensitivity case were considered not related to the drug by the applicant.

Data from published studies and compassionate programs have not identified new AEs. Syncope, nausea, and vomiting were derived from spontaneous reporting in the post-marketing use in the USA. As one single patient experienced five serious adverse reactions within a few minutes after PYLARIFY administration: syncope, nausea, vomiting, dizziness, and headache. Syncope, nausea, and vomiting as not listed in the US SmPC and considered as related to PYLARIFY, and therefore added with a not known frequency.

3.5. Uncertainties and limitations about unfavourable effects

The main identified uncertainties are the following:

Patients with severe renal impairment were not included in the studies so there is lack of data in these patients. Absence of these data is adequately reflected in the product information.

Incorrect image interpretations can have important consequences for the patients. "PET imaging interpretation errors" has been included in the RMP as an important potential risk. Regarding the Important potential risk PET imaging interpretation error, an educational material for Healthcare professionals has been included in the updated RMP v 0.5.

3.6. Effects Table

Table 40. Effects Table for 18F-DCFPyL

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Specificity (Sp)	Clinical setting: **Initial staging** Validation against histology as Standard of Truth (SoT). Comparator: Conventional Imaging Modalities (post-hoc analysis)	% (95% CI) Median (%)	96.3-98.9% (93.6-99.4) Median: 97.9%	Median: 65.1%	Sensitivity (Se) did not reach the prespecified threshold; therefore, it is considered a failed study as Se was a co-primary endpoint together with Sp. Additional evidence and justification for limited staging was provided (Jansen et al. 2021 study).	Osprey Cohort A (Evaluable set, N=252)
PPV			75.0-89.5% (58.9-98.3) Median: 86.7%	Median: 28.3%		
NPV			91.3-93.5% (87.4-96.9) Median: 83.2%	Median: 78.8%		
Sensitivity	Clinical Setting: **Metastatic or Recurrent PCa** Validation against histology as Standard of Truth (SoT).	% (95% CI)	92.9-98.6% (84.0-100)	NA	Heterogeneity population. Cohort B not considered as pivotal, but supportive for the two indications.	Osprey Cohort B (Evaluable set, N=93)
PPV			81.2-87.8% (72.9-95.3)	NA		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
CLR (correct localisation rate), a measure of PPV at patient level	Clinical setting **BCR diagnosis** in patients with negative or equivocal baseline imaging Comparator NA Validation against Standard of Reference, by order of preference, histology or conventional imaging modalities or clinical follow-up.	% (95% CI)	84.8-87.0% (77.8-93.6)	NA	SoR raises concerns about results bias. Specificity at region level was not provided. Local evaluation of PET images instead of central reading was used to determine the SoR. The SoR consisted of only 31 patients with histopathology confirmation, 100 patients with correlative imaging data and only 1 patient with PSA response after radiotherapy (RT). Correlative imaging criteria were subjective. The time for collection of follow-up imaging was only 60 days	Condor study (FAS, N=208)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
DR (detection rate) Number of patients positive at patient level bye IMP among the total patients assessed	Clinical setting **BCR diagnosis** At first recurrence Comparator 18F-FCH Validation against Standard of Reference, by order of preference, histology or conventional imaging modalities or clinical follow-up.	% (95% CI) P-value (Prescott's test)	58.2% (51.4-65.0) P<0.0001	40.3% (33.5-47.1)	SoR raises concerns about the validity of the study. Only 37 patients were assessed per region. SoR consisted of the combination of test available at baseline and performed in clinical routine practice up 10 months after last radiopharmaceutical injection. This follow-up was at discretion of the investigator. No data are provided about the criteria followed to classify each case according to the standard of reference.	Python study (FAS, N=205)
Unfavourable Effects						
TEAEs	In OSPREY, AEs occurring from the day of, but after 18F-DCFPyL administration, through the date of (but prior to) surgery or through 21 (± 7) days post-biopsy. In CONDOR, AEs from the time of administration until the scheduled safety follow-up telephone call 7 (±3)days after dosing. In PYTHON, AEs at the time or during the following 24h after drug administration.	% (n/N)	OSPREY and CONDOR: 11 (65/593) PYTHON: 2 (4/204)	NA	Patients with severe renal impairment were not included in the studies.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Hyper-sensitivity	Incidence in OSPREY and CONDOR population	% (n/N)	0.2 (1/593)	NA	SAE considered related to the drug in OSPREY and CONDOR population.	

Abbreviations: Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV), Standard of Reference (SoR), Prostate Cancer (PCa). Notes: NA

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Conventional imaging modalities (e.g., CT, MRI, whole body bone scintigraphy) are suboptimal for detecting small metastatic lesions or occult locoregional recurrence in patients suffering from PCa.

It is recognised that availability of more sensitive non-invasive diagnostic tool would be important to guide the doctors in decision-making on treatment/patient management in PCa. Although there are uncertainties related to the limited evidence of 18F-DCFPyL PET/CT for primary staging and despite the limitations of the studies, submitted data suggest that 18F-DCFPyL PET/CT may offer improvements in diagnostics of PCa during primary staging of patients at high-risk of metastases and in the staging on patients suffering BCR.

The assessment of the impact on patient management showed considerable effects which could translate into clinical benefit, mainly for BCR patients. For primary staging, caution must be considered when taking therapeutic decisions in absence of prospective studies demonstrating survival benefit. A statement has been added to the SmPC (4.4): To date no outcome data exist to support subsequent management of patients based on PSMA-PET in the primary staging. Therefore, treatment should not be changed based on piflufolastat (18F) PET/CT findings only.

Studies demonstrated good levels of inter-reader agreement when assessing the reliability of the image read.

It is agreed that most SAEs seem related to common conditions in the relatively old male population suffering prostate cancer or/and can be explained by their medical history/underlying diseases, once narratives are revised. No SAEs were reported in study PYTHON. No deaths observed in studies OSPREY, CONDOR or PYTHON.

No critical safety findings were identified. Overall, the safety profile of 18F-DCFPyL appears acceptable.

3.7.2. Balance of benefits and risks

Overall, evidence provided to support efficacy, and the favourable safety profile is considered sufficient to substantiate a positive benefit/risk balance in primary staging of patients at high-risk of metastases and in the staging on patients suffering BCR.

Pylclari may contribute to the diagnostics of PCa during primary staging and diagnosis of PCa recurrence in patients with BCR. Given the low number of safety reports in the literature and in the 3 pivotal studies (PYTHON, OSPREY and CONDOR) and mostly mild severity of the reported AEs, it can be concluded that the benefits outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall benefit/risk balance of Pylclari is positive subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Pylclari is favourable in the following indication(s):

This medicinal product is for diagnostic use only.

Pylclari is indicated for the detection of prostate-specific membrane antigen (PSMA) positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings:

- Primary staging of patients with high-risk PCa prior to initial curative therapy,
- To localize recurrence of PCa in patients with a suspected recurrence based on increasing serum prostate-specific antigen (PSA) levels after primary treatment with curative intent.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Pylclari (piflufolastat (^{18}F)) in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The educational programme is aimed to reduce the risk of PET imaging interpretation errors.

The MAH shall ensure that, in each Member State where Pylclari (piflufolastat (^{18}F)) is marketed, medical practitioners qualified to interpret PET scans in their country who are expected to use Pylclari (piflufolastat (^{18}F)) have access to the self-training educational material.

- Provision of a self-training program containing the following information:

- Physiological distribution of piflufolastat (^{18}F).

- Image interpretation guidelines.

- Examples of incidental findings on PET-CT with piflufolastat (^{18}F).

- Examples of positive and negative findings on PET-CT with piflufolastat (^{18}F)

- Demonstration cases with image interpretation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from PRAC.

New Active Substance Status

Based on the review of available data, the CHMP considered that this radiopharmaceutical is a new active substance as the coupling mechanism to link piflufolastat and fluorine-18 (18F) has not been authorised previously in the European Union.

Refer to Appendix on new active substance (NAS).