EU Risk Management Plan for Pylclari

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 17-Nov-2022

Date of final sign-off: 24-May-2023

Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in this RMP: Not applicable

Other RMP versions under evaluation: Not applicable

Submitted on: May 2023

Procedure number: EMEA/H/C/005520

Details of the currently approved RMP: Not applicable

QPPV's name: Hélène-Eve BORDIER
QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV.

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List of Abbreviations

Abbreviations	Definition of Term
ADT	Androgen Deprivation Therapy
AE	Adverse event
AR	Androgen receptor
ASR	Age-standardised rate
ATC	Anatomical Therapeutic Chemical
BCR	Biochemical recurrence
CLR	Correct localization rate
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EBRT	External beam radiation therapy
EMA	European Medicines Agency
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
FDA	(US) Food and Drug Administration
GLP	Good Loboratory Practice
ICRP	International Commission on Radiological Protection
MAA	Marketing Authorisation Application
MBq	Megabecquerel
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NDA	New Drug Application
PCa	Prostate cancer
PET	Positron Emission Tomography
PSA	Prostate Specific Antigen
PSMA	Prostate Specific Membrane Antigen
PPV	Positive predictive value
RP	Radical prostatectomy
RT	Radiation therapy
SAE	Serious adverse event
SmPC	Summary of product characteristics
SOR	Standard of Reference
SOT	Standard of Truth
TEAE	Treatment-emergent adverse event

Part I: Product(s) Overview

Progenics Pharmaceuticals Inc. and CURIUM have entered into an agreement to develop and commercialize (^{18}F)-DCFPyL in Europe in December 2018.

Progenics Pharmaceuticals Inc. has completed the clinical development of (^{18}F)-DCFPyL in US and submitted a NDA to the FDA in September 2020 to support regulatory approval of (^{18}F)-DCFPyL based on two pivotal clinical trials (OSPREY and CONDOR), CURIUM PET France being a co-development partner. (^{18}F)-DCFPyL imaging agent is now approved in USA from 26May2021 under the trade name PYLARIFY® (Marketing authorization holder: Lantheus Holdings, Inc.*).

CURIUM PET France (dedicated unit for positron emission tomography (PET)), has completed the clinical development of (^{18}F)-DCFPyL CURIUM in Europe, conducting clinical studies and compassionate use programs in the European Economic Area (EEA). CURIUM PET France is planning support investigator-initiated studies and is currently submitting a Marketing Authorisation application of (^{18}F)-DCFPyL CURIUM in Europe.

**: Lantheus Holdings, Inc. is the parent company of Lantheus Medical Imaging, Inc., Progenics Pharmaceuticals, Inc. and EXINI Diagnostics AB*

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	piflufolastat (^{18}F)
Pharmacotherapeutic group(s) (ATC Code)	Diagnostic radiopharmaceuticals, other diagnostic radiopharmaceuticals for tumour detection V09IX16
Marketing Authorisation <Holder> <Applicant>	CURIUM PET France 3 rue Marie Curie Biopôle Clermont Limagne 63360 Saint Beauzire (France)
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Pylclari
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class This diagnostic medicinal product contains the 2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]- pentyl}ureido)-pentanedioic acid (abbreviated as (^{18}F)-DCFPyL).
	Summary of mode of action Prostate-Specific Membrane Antigen (PSMA), is a trans-membrane glycoprotein primarily expressed in some normal human 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}F)-labeled small-molecule PSMA inhibitor. Based on the intensity of the signals, PET images obtained using piflufolastat (^{18}F) DCFPyL CURIUM indicate the presence of PSMA-expressing in tissues. Based on the intensity of the signals, PET images obtained using piflufolastat (^{18}F) indicate the presence of PSMA-expressing in tissues. Physiologic accumulation of piflufolastat (^{18}F) is 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 is with the rest of the body background region. At the chemical concentrations used and the activities recommended for diagnostic examinations, (^{18}F)-DCFPyL CURIUM does not appear to have any pharmacodynamic activity.
	Important information about its composition: (^{18}F)-DCFPyL CURIUM contains fluorine-18 (^{18}F) and piflufolastat (1000 MBq/ml). Each millilitre of solution contains a maximum of 3.5 mg of sodium.
Hyperlink to the Product Information	*common-pidoc*
Indication(s) in the EEA	Current: 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.
	Proposed (if applicable): not applicable
Dosage in the EEA	Current: *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.* *Renal impairment/Hepatic impairment*

	Piflufolastat (^{18}F) has only been studied in patients with mild renal impairment. Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients. Piflufolastat (^{18}F) has not been studied in patients with hepatic impairment. *Paediatric population* There is no relevant use of (piflufolastat (^{18}F) in the paediatric population.
	Proposed (if applicable):
Pharmaceutical form(s) and strengths	Current (if applicable): Solution for injection. Clear, colourless solution with a pH ranging from 4.5 to 7.5. Pylclari 1 000 MBq/mL solution for injection Each mL of solution contains 1,000 MBq of piflufolastat (^{18}F) at the date and time of calibration. The total activity per vial ranges from 500 MBq to 10,000 MBq at the date and time of calibration. Pylclari 1 500 MBq/mL solution for injection Each mL of solution contains 1 500 MBq of piflufolastat (^{18}F) at the date and time of calibration. The total activity per vial ranges from 750 MBq to 15 000 MBq at the date and time of calibration.
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU?	Yes: to be included into the list of additional monitoring as new active substance

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication

This medicinal product is for diagnostic use only.

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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.

Incidence, prevalence and mortality

Incidence

With an estimated 1.4 million new diagnoses and 375,000 deaths worldwide, prostate cancer (PCa)is the second most frequent malignancy (after lung cancer) and the fifth leading cause of cancer death among men in 2020 (Ferlay et al., 2021, 2020). The incidence of PCa diagnosis varies widely between different geographical areas, being highest in Australia/New Zealand and Northern America (age-standardised rates [ASR] per 100,000 of 111.6 and 97.2, respectively), and in Western and Northern Europe (ASRs of 94.9 and 85, respectively) (Mottet et al., 2021). The reason for these differences among the countries is not entirely clear but are likely due to the use of prostate-specific antigen (PSA) testing and the aging population (Rawla, 2019).

In Europe, there were an estimated 473,000 new diagnoses and 108,000 deaths in 2020 making it the 1st commonly diagnosed cancer and the 3rd most common cause of cancer-related death in men, with an annual incidence that continue to rise. The recent PCa incidence rate in France was among the highest rates in Europe, counting an estimated 66,000 new cases that represent an ASR of 99 per 100,000 patients in 2020 (Ferlay et al., 2020).

Prevalence

Although PCa incidence rates are high, most PCa cases are detected when the cancer is at localized stage. Localized prostate cancer is frequently indolent and portends a good prognosis even if left untreated. The data from the Eurocare project (EUROCARE-5) of patients diagnosed with prostate cancer from 2003 to 2007 showed a 5-year survival rate of 83%. Survival varied from 76% in Eastern countries to 88% in Southern and Central European countries (De Angelis et al., 2014). Moreover, survival has increased over time in all over Europe with the greatest improvement being observed in the Eastern European countries (Rawla, 2019). A recent meta-analysis of 29 studies reported an estimated mean

cancer prevalence at age < 30 years of 5% (95% confidence interval (CI): 3–8%), which increased nonlinearly to 59% (95% CI: 48–71%) by age > 79 years (Bell et al., 2015).

Demographics of the population and risk factors

The well-established risk factors for PCa are age, family history with true hereditary disease or not and ethnicity (Culp et al., 2020; Mottet et al., 2021; Rawla, 2019).

Age – Primarily a disease of the elderly, the median age at diagnosis of PCa is 68 years. PCa incidence increases with age. Although only 1 in 350 men under the age of 50 years will be diagnosed with PCa, the incidence rate increases up to 1 in every 52 men for ages 50 to 59 years. The incidence rate is nearly 60% in men over the age of 65 years. This largely reflects cell DNA damage accumulating over time. Damage can result from biological processes or from exposure to risk factors ("Prostate Cancer (C61), Average Number of New Cases per Year and Age-Specific Incidence Rates, UK, 2016-2018," n.d.).

Ethnicity - Worldwide, African-American men are the most likely to develop PCa and are also more likely to develop the disease at a younger age, with high rates evident in Afro-Caribbean men and those of West African origin. Hispanics are at lower risk than Caucasians, as are those from South-East Asia. The reasons for these differences are unclear but appear to reflect both genetic predisposition and environmental factors, including diet and socioeconomic conditions (Mottet et al., 2021; Rawla, 2019; Rosario and Rosario, 2022).

Family history - Only a small subpopulation of men with PCa have true hereditary disease. Hereditary PCa (HPCa) is associated with a six-to-seven-year earlier disease onset but the disease aggressiveness and clinical course does not seem to differ in other ways (Jansson et al., 2012; Randazzo et al., 2016).

Beyond age, genetic and socioeconomic factors, a wide variety of individual, environmental, and occupational risk factors are also proposed to justify differences in the epidemiological burden of the disease, including dietary factors, hormonally active medication and co-morbidities such as metabolic syndrome, diabetes and obesity (Rawla, 2019).

Main diagnostic options

Several imaging modalities are currently employed for the diagnosis, staging, re-staging and the determination of prognosis in PCa patients. Conventional cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) are among the most widely used methods, but both have clinically relevant limitations especially in low volume disease (e.g., patients with biochemical recurrence [BCR]). 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., 2007; Scheidler et al., 1999; Shinohara et al., 1989).

Comparable limitations exist for currently used functional imaging methods in nuclear medicine. Radionuclide bone scans and ^{18}F-fluorocholine (or ^{18}F-fluciclovine) PET/CT are commonly used diagnostic methods in prostate cancer patients. However, as bone scans detect tissue remodelling, as opposed to tumour burden, false positive results can be caused by inflammation, previous bone injuries, and arthritis. ^{18}F-fluorocholine has been reported as comparably sensitive to ^{18}F-sodium fluoride (NaF) PET for detection of bone metastases (Beheshti et al., 2009; Langsteger et al., 2011). However, it is not regarded as sufficiently sensitive for detection of metastases in other body regions (Bauman et al., 2012).

^{18}F-Fluorocholine and ^{18}F-fluciclovine, are not reliable in patients with low PSA levels (<2.0 ng/mL) (Calais et al., 2019; Evans et al., 2018; Nanni et al., 2016), which represents a large and growing proportion of patients presenting with recurrent or metastatic disease. The per-patient sensitivity of ^{18}F-fluorocholine was as low as 33% for detection of lymph node metastases in 112 patients examined for prostate cancer staging (Kjölhede et al., 2014); and the detection rate was dependent on PSA value in BCR with low detection rates below a PSA of 2 ng/mL.

Natural history of the disease

As previously discussed, localized PCa is frequently indolent and has an excellent prognosis. Patients with high-grade, high-volume cancer are more likely to progress to locally advanced and metastatic disease, but risks can be mitigated by early detection and treatment. Determining the PCa staging is essential to decide on the treatment for high-risk forms. Rising PSA after initial definitive therapy (known as first BCR) of PCa may occur in 20-30% of patients within 5 years, before a more definitive diagnosis of metastatic disease can be established by conventional imaging modalities (Afshar-Oromieh et al., 2015; Cookson et al., 2007; Roach et al., 2006; Roehl et al., 2004). 20–40% of patients undergoing radical prostatectomy (RP) and 30–50% of patients undergoing external-beam radiation therapy (EBRT) will experience BCR within 10 years (le Guevelou et al., 2021; Paller and Antonarakis, 2013).

The key question in case of BCR remains whether the PSA rise is reflective of locally confined recurrence or is caused by distant metastatic disease.

Due to increasing life expectancy and the introduction of more sensitive diagnostic screening techniques, PCa is being diagnosed more frequently and the worldwide variations in PCa incidence might be attributed to PSA testing. It has a wide spectrum of biological behaviour, ranging from indolent low-risk disease to highly aggressive castration-resistant PCa. According to recently conducted research studies, around 20-40% of the PCa cases in the USA and Europe could be due to overdiagnosis through extensive PSA testing.

Important co-morbidities:

Co-morbidities are consistent with the risk factor profil of the disease and the advanced age of the target population (men older than 50). Co-morbidity is more important than age in predicting life expectancy in men with PCa. Increasing co-morbidity greatly increases the risk of dying from non-PCa-related causes and for those men to have a short life expectancy (Albertsen et al., 2011; Jefferson et al., 2020; Mottet et al., 2021; Tewari et al., 2004).

Co-morbid conditions to be considered are:

- diabetes,
- hypertension,
- heart disease
- stroke,
- moderate to severe chronic obstructive pulmonary disease,
- hypercholesterolemia,
- depression, anxiety,
- liver disease,
- history of alcoholism,
- renal failure,

- mobility disability with assistive equipment

Compared with men without any comorbidities, a higher hazard rate for non-PCa mortality was identified among men with diabetes without end-organ damage (HR 2.32; 95% CI 1.32–4.08), peripheral vascular disease (HR 2.77; 95% CI 1.14–6.73), moderate-severe chronic obstructive pulmonary disease (HR 5.46; 95% CI 2.68–11.12), diabetes with end-organ damage (HR 4.27; 95% CI 1.64–11.10), those in need of a mobility device (HR 3.29; 95% CI 1.87–5.80), and men with history of alcoholism (HR 1.77; 95% CI 1.07–2.93) (Chamie et al., 2012).

Concomitant medications in the target population

In patients, PCa drugs and androgen deprivation therapy (ADT) or other androgen receptor (AR)-targeted treatments, male sex hormones, and antagonists as well as lidocaine/lignocaine in anaesthesia were commonly used, especially after cancer diagnosis. While there was no concomitant use of ADT in patients enrolled in one US study (CONDOR), 55 patients (26.4%) had prior treatment with ADT. No difference was observed in the correct detection rate of (^{18}F)-DCFPyL in patients previously treated with ADT compared with those without prior treatment.

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

Finally, in PYTHON study, while prior ADT was an exclusion criterion, 27 (13.2%) patients were previously treated with ADT at least 30 days before PSMA imaging.

Recent history of chemotherapy, radium-223 or ^{177}Lu-PSMA-targeted radioligand therapy should also be considered.

As well, prior administration of Furosemide in some circumstances (i.e. when immediate voiding before image acquisition is difficult), can be done to prevent high residual activity in the urinary system which might lead to so-called "halo artefacts" in PET. Activity in ureters might lead to false positive findings.

In the primary staging population, there were 20/252 (7.9%) evaluable patients in the US study OSPREY Cohort A identified as concurrent diuretic users. In the recurrent PCa population there were 15/93 (16.1%) and 24/208 (11.5%) evaluable patients identified with concurrent diuretic use in OSPREY Cohort B and in CONDOR respectively. The use of diuretics at the time of dosing does not appear to impact the diagnostic performance of (^{18}F)-DCFPyL injection in newly diagnosed PCa patients or patients with recurrent or metastatic disease. Among the 205 patients randomised in PYTHON study, 148 (72.2%) patients were taking at least one concomitant medication. The most frequent concomitant medications were: agents acting on the renin-angiotensin system in 72 (35.1%) patients, lipid modifying agents in 69 (33.7%) patients, antithrombotic agents in 61 (29.8%) patients, beta blocking agents in 39 (19%) patients, drugs for acid related disorders in 39 (19%) patients, drugs used in diabetes in 33 (16.1%) patients, and calcium channel blockers in 31 (15.1%) patients.

It should be noted that PSMA expression is physiologically upregulated after the beginning of ADT (Wright et al., 1995). Androgen receptor (AR) inhibition is believed to increase PSMA expression in PCa. This upregulation and its exact timing are not completely understood but must be considered to prevent falsely defining disease progression shortly after initiation of AR-targeted therapies (Aggarwal et al., 2018; Emmett et al., 2019).

A similar reaction is hypothesized for the use of second-generation AR targeted therapies (e.g. enzalutamide, abiraterone). Caution has to be taken when interpreting an increase (or potentially a decrease) in PSMA expression shortly after start of a new AR-targeted therapy (Evans et al., 2011). PSMA expression and, therefore, PSMA PET uptake on serial imaging may be affected by sensitivity or resistance of PCa to ADT and needs further validation. Regarding taxane-based chemotherapy, preclinical data indicate that intensity of PSMA expression can serve as a surrogate parameter for therapy response (Hillier et al., 2011).

Part II: Module SII - Non-clinical part of the safety specification

Nonclinical Testing Strategy

(^{18}F)-DCFPyL is a microdose radiopharmaceutical diagnostic agent. The maximum chemical mass of DCFPyL associated with the clinical dose of 330 MBq (9 mCi) is ≤ 4 µg, with a maximum theoretical instantaneous blood concentration of ≤ 18 nM. Due to the very low chemical mass dose to be administered, European Medicines Agency (EMA) and Food and Drug Administration (FDA) provided specific guidance for microdose radiopharmaceutical diagnostic drugs on nonclinical studies (European Medicines Agency (EMA), 2018, 2009; Research, 2020). These guidelines/guidances recommend that safety pharmacology, repeat-dose toxicity, genotoxicity and special toxicity studies are not needed. Furthermore, EMA accepts the use of extended single-dose toxicity studies in one species to support single-dose clinical trials in humans.

The nonclinical data package developed based on EMA guideline (European Medicines Agency (EMA), 2018, 2009) was presented to support the Pylclari Marketing Authorisation Application (MAA). The primary pharmacology, pharmacokinetics, as well as PET imaging data of Pylclari were investigated *in vitro*, ex vivo and in vivo in mouse xenograft models and are described in literature. An extended single dose toxicity study was also conducted in rats (report SB-MP-001). Based on the scientific advice from CHMP, EMA, provided during July 2019, the applicant also performed *in silico* evaluation of potential mutagenicity of Pylclari.

Thus, based on the guidelines and recommendations from the Agency, the nonclinical testing strategy to support the current Pylclari MAA is adequate, including pharmacology and pharmacokinetic data from a published report, (Chen et al., 2011; Roy et al., 2021), Module 2, Sections 2.6.2 and 2.6.4, respectively), as well as an extended 14-day single dose toxicity study in rats (Module 2, Section 2.6.6).

Table SII.1 summarises the key nonclinical findings and their relevance to safety in humans.

No safety concerns have been identified.

Table SII.1. Overview of Non-Clinical Studies

Key Safety Findings Non-Clinical (from Non-Clinical Studies)	**Relevance to Human Usage**
Toxicity Studies	
Single-Dose Toxicity (extended 14-day single dose toxicity in one species as agreed by FDA/EMA) An extended single dose Good Laboratory (GLP) study was conducted to evaluate the toxicity of (^{18}F)-DCFPyL on days 3 and 15 following a single IV dose in rats. Male and female Sprague Dawley rats were assigned to six (6) groups (N=5/gender/group) and dosed IV on day 1 with 0.1 or 0.5 mg/kg (^{18}F)-DCFPyL or vehicle control. Assessment of toxicity was based on mortality, clinical signs, body weight, body weight changes, and clinical and anatomic	No treatment related findings were identified further to the single-dose toxicity study. No animal showed any adverse reactions. This medicinal product being not intended for regular or continuous administration, no long-term toxicity

pathology. Separate set of animals were sacrificed on day 3 and 15. No test article-related observations were noted in body weight or cage side behavior of the animals during the study, and all rats survived to scheduled termination. No statistically significant or treatment-related differences were noted in the clinical chemistry or organ weight data at Study Day 3 or 15. Microscopic findings in tissues obtained from Study Day 3 and Day 15 rats were considered incidental and not directly related to the test article. In conclusion, under the conditions of this study, there were **no treatment related findings** in Sprague Dawley rats three or fifteen days after a single IV dose of (^{18}F)-DCFPyL at 0.1 mg/kg and 0.5 mg/kg. The recommended human dose of (^{18}F)-DCFPyL is 330 MBq (9 mCi) which contains a chemical mass of ≤ 40 micrograms of (^{18}F)-DCFPyL. 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, suggesting adequate safety margin. **Genotoxicity** According to US FDA and EMA guidelines as referred above, genotoxicity studies are not required for radiodiagnostics. Based on the scientific advice from CHMP, EMA, provided during July 2019, the applicant also performed *in silico* evaluation of potential mutagenicity of (^{18}F)-DCFPyL. An *in silico* computational evaluation of (^{18}F)-DCFPyL was performed using DEREK Nexus, an expert knowledge-based tool and Sarah Nexus, a statistical-based tool. There was no structural alert for mutagenicity in bacteria and the prediction by both tools were negative suggesting no mutagenic concern with (^{18}F)-DCFPyL.	with repeated administration or carcinogenesis have been tested. There was no structural alert for mutagenicity in bacteria and the prediction by both tools were negative suggesting no mutagenic concern with Pylclari
Safety pharmacology	
Safety pharmacology studies were not conducted in accordance with US FDA/EMA Guidance on microdose radiopharmaceutical diagnostic drugs.	Pylclari is a second-generation fluorine-18-labeled small-molecule PSMA inhibitor binding PSMA. The maximum human mass dose of (^{18}F)-DCFPyL is 40 micrograms.

There was a relatively low bone uptake of radioactivity, suggesting little metabolic de-fluorination of (^{18}F)-DCFPyL occurred in mice. Indeed, Szabo et al. showed that no metabolism of (^{18}F)-DCFPyL was observed on radio-HPLC analysis following IV administration in a first in human study (Szabo et al., 2015). The safety data from clinical studies and the use of approved products containing (^{18}F)-DCFPyL do not suggest any safety concerns.	At the chemical concentrations used and the activities recommended for diagnostic examinations, Pylclari does not appear to have any pharmacodynamic activity.
Other toxicity-related information or data	
Dosimetry concern The mouse biodistribution data from the study by Chen et al. (Chen et al., 2011), showed rapid and high uptake in the kidney (74.1±6.6%ID/g at 30 minutes decreasing to 7.4±0.9%ID/g at 4 hours), as well as extensive bladder exposure, following IV injection of (^{18}F)-DCFPyL suggesting a urinary clearance for (^{18}F)-DCFPyL in mice. Indeed, in a phase 1 study by Szabo et al. (Szabo et al., 2015), (^{18}F)-DCFPyL did not appear to undergo meaningful metabolism. Coupled with the concomitant high uptakes in the kidney and bladder, further supports that (^{18}F)-DCFPyL is renally excreted following IV administration in men with PCa. To estimate the human radiation dosimetry values, the mouse organ activity concentrations in %ID/g were converted to the human %ID/organ by setting the ratio of organ %ID/g to whole-body %ID/g in the mouse equal to that in humans and then solving for the human %ID/organ. Based on the dosimetry results in mice, it was estimated that a maximum of 9 mCi (330 MBq) could be administered without exceeding the 50 mGy critical organ dose limit (kidneys, liver and spleen in this case).	Knowledge on dosimetry and physiological uptake is important. (^{18}F)-DCFPyL is renally excreted following IV administration in men with prostate cancer. The effective dose resulting from the administration of an activity 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. The target tissue is PSMA-expressing tumors that are not just limited to prostate gland but could be located elsewhere in the body.

Part II: Module SIII - Clinical trial exposure

Completed clinical studies

Progenics and CURIUM have completed three (3) prospective, multi-center, multi-reader (central, independent, blinded readers), well-controlled clinical trials, Study PyL2301 (OSPREY), Study PyL3301 (CONDOR), and EudraCT 2020-000121-37 (PYTHON) that evaluated the diagnostic performance of (^{18}F)-DCFPyL PET imaging for the detection of PCa across the continuum of disease states from patients with high risk disease at initial diagnosis to patients with disease recurrence and metastases, based primarily on histopathology as the truth standard.

OSPREY is a phase 2/3 study conducted to evaluate the diagnostic performance of (^{18}F)-DCFPyL PET imaging in two PCa patient populations that provided tissue for histopathology as the truth standard: Cohort A enrolled patients with high-risk PCa planned for surgery as initial therapy, and Cohort B enrolled patients with presumptive radiologic evidence of recurrent or metastatic PCa on conventional imaging that was feasible for biopsy.

CONDOR is a phase 3 study conducted to evaluate the diagnostic performance of (^{18}F)-DCFPyL PET imaging in patients with recurrent or metastatic PCa based on BCR with negative or equivocal baseline imaging.

PYTHON is a phase 3 European study sponsored by CURIUM PET France and conducted to evaluate the performances (^{18}F)-DCFPyL PET imaging in first BCR in patients with histopathologically confirmed PCa per original diagnosis, who underwent definitive therapy (RP, EBRT or brachytherapy).

Protocol number/ EudraCT	**PyL 2301 (OSPREY) NCT02981368**	**PyL 3301 (CONDOR) NCT03739684**	**EudraCT number 2020-000121-37 PYTHON study**
Name and address of the sponsor	PROGENICS	PROGENICS	CURIUM PET FRANCE
Study design	Multicenter, phase 2/3, open-label, nonrandomized, controlled study	Multicenter, phase 3, open-label, single-arm, nonrandomized, controlled study	Multicenter, phase 3, open-label, cross-over, randomized, controlled study
Study Start - End Date	30 November 2016 - 19 July 2018	30 November 2018 - 29 August 2019	01 July 2020 – 17 December 2020
Status	Closed	Closed	Closed
Number of Centers/ Countries involved	United States: 8 sites Canada: 2 sites	United States: 13 sites Canada: 1 site	EU : 22 sites (France, Spain, Belgium, Netherlands)
Study title	A Prospective Phase 2/3 Multi-Center Study of (^{18}F)-DCFPyL PET/CT Imaging in Patients with Prostate Cancer: Examination of Diagnostic Accuracy (OSPREY)	A Phase 3, Multi-Center, Open-Label Study to Assess the Diagnostic Performance and Clinical Impact of (^{18}F)-DCFPyL PET/CT Imaging Results in Men with Suspected Recurrence of Prostate Cancer (CONDOR)	A Prospective Study on (^{18}F)-DCFPyL PET/CT Imaging in Biochemical Recurrence of Prostate Cancer

Study Primary Objective	To assess the diagnostic performance of (^{18}F)-DCFPyL PET/CT imaging to determine the presence or absence of pelvic lymph node metastases in pre-prostatectomy patients with at least high-risk prostate cancer (cohort A)	To evaluate the correct localization rate, clinical utility, and safety of (^{18})F-DCFPyL (PyL) PET/CT imaging in patients with biochemical recurrent (BCR) prostate cancer	Prospective, open label, cross-over, order of injection randomized, central image evaluation, order of blinded read sessions randomized To compare the per-patient detection rate of (^{18}F)-DCFPyL PET/CT versus that of (^{18}F)-FCH PET/CT
Dose and regimen	9 ± 1 mCi (333 ± 37 MBq) as a single IV injection	9 mCi (333 MBq) ± 20% as a single IV injection	one single intravenous injection of 330 MBq of (^{18}F)-DCFPyL (range 300-360)
Study population	Eligible subjects with at least *high-risk* prostate cancer defined by NCCN (v3.2016) who were planned for radical prostatectomy with pelvic lymph node dissection (cohort A) and subject with radiologic evidence of l*ocal recurrence or new or progressive metastatic* disease (cohort B)	Men ≥ 18 years of age, with a life expectancy of ≥6 months, who provided informed consent, were eligible if they had histopathologically confirmed prostate adenocarcinoma, had *suspected recurrent or metastatic* prostate cancer based on rising PSA levels after prior initial definitive therapy, and had negative or equivocal findings for prostate cancer on conventional imaging within 60 days prior to Day 1. Patients were ineligible if they were currently undergoing systemic therapy, or they had received a high-energy gamma-emitting radioisotope within 5 physical half-lives, treatment with ADT within 3 months, or investigational therapy for prostate cancer within 60 days of Day 1.	*First BCR* in patients with histopathologically confirmed prostate adenocarcinoma per original diagnosis, who underwent definitive therapy (prostatectomy, external beam radiotherapy or brachytherapy).
Age: Mean (Range) in Years and Sex (M/F)	65.2 (45 – 86) years 100% Male	67.9 (43 – 91) years 100% Male	70.0 (53 – 88) years 100% Male
Number of patients recruited	385	208	217 patients recruited, 215 randomised (2 were not randomised due to exclusion criteria)
Number of patients completed	385	208	205 patients (204 with (^{18}F)-DCFPyL and 202 with ^{18}F-Choline)
Recruitment completed	No ❒ Yes ☒	No ❒ Yes ☒	No ❒ Yes ☒
Methodology of Adverse Events Reporting	Changed so that treatment-emergent adverse events (TEAEs) would be recorded from the day of study drug administration until 7 (±3) days after study drug injection (if surgery [Cohort A] or biopsy [Cohort B] had not yet occurred) and 21 (±7) days post-biopsy in Cohort B	Adverse events (AEs) were assessed following (^{18}F)-DCFPyL dosing (Day 1), and again via a safety phone call 7 (±3) days post (^{18}F)-DCFPyL dosing to capture any late-occurring AEs.	Adverse events observed, mentioned upon open questioning, or spontaneously reported will be recorded during the first 24 hours following each injection. SAEs reported according to ICH-GCP.

A total of 797 patients were administered with (^{18}F)-DCFPyL in the clinical development program: 208 in CONDOR, 385 in OSPREY and 204 in PYTHON.

A tabular summary of subjects who received any amount of (^{18}F)-DCFPyL for each study by age is provided in Table SIII.1 (for CONDOR, OSPREY and PYTHON).

Table SIII.1: Estimated Cumulative Drug Exposure (by Study) to (^{18}F)-DCFPyL Injection by Age Group (Safety Population)

Study	Age (yrs)		Total
	<65 n (%)	≥65 n (%)	
CONDOR	67 (32.2)	141 (67.8)	208
OSPREY	171 (44.4)	214 (55.6)	385
Cohort A	*132 (49.3)*	*136 (50.7)*	*268*
Cohort B	*39 (33.3)*	*78 (66.7)*	*117*
PYTHON	49 (23.9)	156 (76.1)	205*
Total	287	511	798

*:204 patients administered with (^{18}F)-DCFPyL

Table SIII.2: Administered dose (all indications)

Study	Patients (n)	Median Dose of exposure (MBq) (range)
OSPREY and CONDOR	593	340.4 (236.8, 410.7)
PYTHON	*188 (17 missing values)*	Median: 321.19 [186.9* - 373.0]
Total	*781 (98%)*	NA

*: low activity administered in one patient due to product delivery issue.

Table SIII.3: Estimated Cumulative Drug Exposure (by Study) to (^{18}F)-DCFPyL Injection by Proposed Indication (Safety Population)

Indication	Patients n *(%)*
Staging – High risk PCa (OSPREY Cohort A)	268 *(33.6)*
Recurrent or Metastatic PCa (CONDOR, OSPREY Cohort B, PYTHON)	529 *(66.4)*
Total	*797 (100)*

Table SIII.4: Summary of Treatment Emergent Adverse Events, Safety Set

Indication	**Staging – High risk PCa (OSPREY Cohort A)** n *(%)*	**Recurrent or Metastatic PCa (CONDOR, OSPREY Cohort B, PYTHON)** n *(%)*
Patients	268	529
Any TEAE	39 (14.6)	14 (6.7) CONDOR 12 (10.3) OSPREY Cohort B **6 (2.9)** PYTHON
Any study drug related TEAE	25 (9.3)	3 (1.4) CONDOR 2 (1.7) OSPREY Cohort B 0 PYTHON
Any TEAE CTCAE Grade ≥3	1 (0.4)	1 (0.5) CONDOR 4 (3.4) OSPREY Cohort B 1 (0.5) PYTHON
Any related TEAE CTCAE Grade ≥3	1 (0.4)	1 (0.5) CONDOR 0 OSPREY Cohort B 0 PYTHON
Any TEAE leading to study drug interruption or discontinuation	0	0 OSPREY Cohort B 0 PYTHON
Any SAE	1 (0.4)	1 (0.5) CONDOR 6 (5.1) OSPREY Cohort B 0 PYTHON
Fatal SAE	0	0 OSPREY Cohort B 0 PYTHON

AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events (version 4.0), SAE = serious AE, TEAE = treatment-emergent AE.

OSPREY Cohort A (**staging**): Single, 9 mCi (333 MBq) doses of (^{18}F)-DCFPyL were well tolerated in this study. The incidence of TEAEs was low (14.6%), and the vast majority were Grade 1 or Grade 2 in severity. A total of 9.3% of patients had a TEAE that was considered by the Investigator to be related to study drug. The majority of AEs were consistent with the patients' advancing age, comorbidities, or expected with radiotracer imaging.

The most common TEAEs (>1% of patients) of any severity grade were dysgeusia (n=9, 3.4%), headache (n=9, 3.4%), and fatigue (n=5, 1.3%). Drug-related TEAEs were reported in 25 (9.3%) patients. Dysgeusia (2.6%) and headache (3.0%) were the most frequently reported drug-related TEAEs.

No patient had a Grade 4 or Grade 5 (fatal) TEAE or discontinued from the study due to a TEAE. One grade 3 event (headache) occurred in 1 patient (0.4%).

CONDOR and OSPREY Cohort B (**Recurrent or Metastatic PCa**) Single, 9 mCi (333 MBq) doses of (^{18}F)-DCFPyL were well tolerated in this study. The incidence of TEAEs were very low (6.7% and 10.3% respectively), and almost all events were Grade 1 or Grade 2 in severity.

-In CONDOR, a total of 6.7% of patients had a TEAE that was considered by the Investigator to be related to study drug. The most common TEAEs (>1% of patients) of any severity grade were headache (n=4, 1.9%), fatigue (n=2, 1.0%) and hypertension (n=2, 1.0%).

The only drug-related TEAEs were headache (Grade 1), fatigue (Grade 1), and hypersensitivity (Grade 3), experienced by a total of 3 (1.4%) patients. Grade 3 TEAEs (headache, paresthesia, and hypersensitivity) were reported in 1 patient (0.5%) and were reported as SAEs for this same patient. No patients had a Grade 4 or Grade 5 event. Only 1 patient (0.5%) reported SAEs (all Grade 3), which were hypersensitivity (drug related), headache, and paresthesia (both unrelated to study drug). This patient had an extensive history of allergic reactions.

-In OSPREY Cohort B, a total of 1.7% of patients had a TEAE that was considered by the Investigator to be related to study drug.

Dysgeusia (0.9%), arthralgia (0.9%), and coronary artery disease (0.9%) were the most frequently reported TEAEs, regardless of relationship to study drug. The only drug-related TEAEs was dysgeusia (Grade 1).

PYTHON (**Recurrent or Metastatic PCa**): Single, 321.19 MBq median injected dose of (^{18}F)-DCFPyL (ranging from 186.9 MBq to 373.0 MBq) was well tolerated in this study.

Only six (6) treatment emergent adverse events (TEAE) were reported during the study in four (4) patients with (^{18}F)-DCFPyL. To note, 3/6 events reported with (^{18}F)-DCFPyL were reported by one same patient. The incidence of TEAEs was very low (2.9%) and almost all events were mainly Grade 1 in severity (Headache, fatigue, eczema and Limb discomfort) and one was grade 3 (hypertension). All these events were deemed as unlikely related to the study drug and were all consistent with patient profile regarding their age, PCa stage and medical histories, notably regarding hypertension. None of these TEAEs were serious. Five (5) recovered and for one (1) the outcome was unknown.

None of the events reported were related to treatment ((^{18}F)-DCFPyL), nor were considered as serious or led to study discontinuation.

(^{18}F)-DCFPyL was safe and well tolerated. Only non-serious and not-related adverse events were reported. No new safety signal was detected.

Please refer to the table SIII.5 below.

Table SIII.5: Display of adverse events in PYTHON study

Study participant	Preferred Term (PT)	TEAE	Severity	Seriousness	Relationship to study treatment	Action taken	Outcome
One study participant	Headache	Yes	Grade 1 - Mild	No	Unlikely	Not applicable	Recovered/Resolved
One study participant	Headache	Yes	Grade 1 - Mild	No	Unlikely	Not applicable	Recovered/Resolved
	Fatigue	Yes	Grade 1 - Mild	No	Unlikely	Not applicable	Recovered/Resolved
	Eczema	Yes	Grade 1 - Mild	No	Unlikely	Not applicable	Recovered/Resolved
One study participant	Limb discomfort	Yes	Grade 1 - Mild	No	None	Not applicable	Recovered/Resolved
One study participant	Hypertension	Yes	Grade 3 - Severe	No	None	Not applicable	Unknown

Patients with recurrent or metastatic prostate cancer may present with prior (or concurrent) ADT use as well as low blood PSA levels.

As there has been some debate as to whether ADT has an effect on PSMA imaging, subgroup analyses by ADT use, demonstrate that prior or ongoing use of ADT in patients with recurrent or metastatic prostate cancer does not appear to impact the performance of (^{18}F)-DCFPyL PET for detecting prostate cancer.

Table SIII.6: Prior ADT administration in patients with recurrent or metastatic PCa

Parameter	CONDOR N= 208 patients	OSPREY Cohort B N=117 patients	PYTHON N=205 patients
Patient **without** androgen deprivation therapy (ADT), n (%)	153 (73.6)	45 (38.5)	176 (85.9%)
Patient **with** androgen deprivation therapy (ADT), n (%)	55 (26.4)	72 (61.5)	27 (13.2%)

In CONDOR, 55 (26.4%) patients had a history of ADT use before PSMA imaging. The positive predictive value (PPV) (or CLR (correct localization rate for positive scans)) was 90% to 94% across the three central readers. In OSPREY Cohort B, 60 (65%) of evaluable patients had prior or ongoing ADT at time of imaging; PPV was 86% to 90% across the three central readers. As reflected by the similar detection rate and consistently high PPV in these patients to the overall performance in all patients for CONDOR and for OSPREY Cohort B, ADT does not appear to affect the diagnostic performance of (^{18}F)-DCFPyL PET imaging for detecting recurrent or metastatic PCa.

In PYTHON, only 27 (13.2%) patients had prior ADT at least 30 days before PSMA imaging. Time since ADT initiation 5.82 [2.14-9.5] years. Mean treatment duration was of 13.08 [0.0-42.5] months.

However, it should be noted that PSMA expression is physiologically upregulated after the beginning of ADT (Wright et al., 1995). Androgen receptor (AR) inhibition is believed to increase PSMA expression in PCa. This upregulation and its exact timing are not completely understood but must be considered to prevent falsely defining disease progression shortly after initiation of AR-targeted therapies (Aggarwal et al., 2018; Emmett et al., 2019).

A similar reaction is hypothesized for the use of second-generation AR targeted therapies (e.g. enzalutamide, abiraterone). Caution has to be taken when interpreting an increase (or potentially a decrease) in PSMA expression shortly after start of a new AR-targeted therapy (Evans et al., 2011). PSMA expression and, therefore, PSMA PET uptake on serial imaging may be affected by sensitivity or resistance of prostate tumours to ADT and needs further validation. Regarding taxane-based chemotherapy, preclinical data indicate that intensity of PSMA expression can serve as a surrogate parameter for therapy response (Hillier et al., 2011).

Ongoing clinical study

In June 2019, PROGENICS initiated a multicenter, phase 2 trial in Canada that uses (^{18}F)-DCFPyL PET/CT to select PSMA-avid subjects with mCRPC who may benefit from PSMA-targeted radioligand therapy with I-131-1095 (1095-2301 [ARROW]). This study was subsequently initiated in the US in January 2020. The ARROW study is ongoing in the US and Canada.

134 patients have received (^{18}F)-DCFPyL in study 1095-2301 [ARROW] as of 17-Nov-2022.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Participants were excluded from the studies according to the general criteria listed below. Detailed descriptions of all exclusion criteria are provided in the individual protocols.

Table SIV.1: Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing information (Yes/No)	Rationale (if not included as missing)
Patients administered any high energy (>300 keV) gamma-emitting radioisotope within 5 physical half-lives prior to study drug (CONDOR and OSPREY)	Prior administration of any high energy (>300 keV) gamma-emitting radioisotope within 5 physical half-lives was one of the important exclusion criteria in both pivotal studies. Reason for exclusion was based on the expected image reading pollution due to interaction between both administered gamma-emitting radioisotopes.	No	Exclusion criteria required for imaging purposes issues, not to possible safety issues.
Patients with prior androgen-deprivation therapy or any investigational neoadjuvant agent or intervention (OSPREY Cohort A and CONDOR)	Inclusion of "de novo" patients for primary staging of PCa. Therefore, patients should not have been treated with any therapeutic options.	No	Exclusion criterion was mainly driven by inclusion criteria.
Prior radiation or ablative therapy to intended site of biopsy, if within the prostate bed. Initiation of new systemic therapy for recurrent and/or progressive metastatic disease since radiographic documentation of recurrence/progression (OSPREY Cohort B)	Prior radiation or ablative therapy to intended site of biopsy, if within the prostate bed: the SOT was anatomopathology. Therefore, no treatment should have been applied to the prostate bed, in order to obtain relevant data. Tissues may be affected by surgery (cicatricial tissues) and by radiation (inflammatory tissues). Initiation of new systemic therapy for recurrent and/or progressive metastatic disease since radiographic documentation of recurrence/progression. Radiographic progression is used as composite SOT. Therefore, any ongoing treatment may affect radiographic results and compromise SOT.	No	The exclusion of prior therapy was linked to the assessment of primary criterion of efficacy, not to possible safety issues.

Previous salvage therapies (including salvage radiotherapy or salvage lymph node dissection) History of adjuvant radiotherapy History of cryotherapy, high-intensity focused ultrasound (HIFU) (PYTHON study)	The studied population being "*First BCR in patients with histopathologically confirmed prostate adenocarcinoma per original diagnosis, who underwent definitive therapy (prostatectomy, external beam radiotherapy or brachytherapy)"* Salvage therapy (surgery/radiation) means that the patient is not at first BCR. Cryotherapy and HIFU are not considered as curative therapy.	No	Exclusion criteria were mainly driven by inclusion criteria (first BCR after initial curative therapy). Therefore, all other situations were considered as exclusion criteria.
Other active malignant tumour (PYTHON study)	Other active malignant tumor might mimic prostate cancer lesions on PET/CT.	No	To avoid any misinterpretation issue. Please refer to Part II SVII.
Treatment with colchicine in the past 8 days or ongoing Treatment with hematopoietic colony stimulating factors (CSF) in the past 5 days or ongoing (PYTHON study)	Colchicine may impair uptake of fluorocholine (^{18}F) (comparative drug) by prostate cancer cells and may lead to false negative results. Colony stimulating factors (G-CSF or erythropoietin) may interact with fluorocholine (^{18}F) (comparative drug) by increasing bone marrow uptake of fluorocholine (^{18}F). This could affect the detection of metastatic osteomedullar foci.	No	Treatment with colchicine or CSF are contra-indications for 18F-fluorocholine. Due to the cross-over design, each patient received (^{18}F)-DCFPyL and (^{18}F)-fluorocholine. Therefore, these interactions are not considered relevant for (^{18}F)-DCFPyL only, this tracer has a different mode of action.
Known allergy to investigational or reference products or to any excipients (PYTHON study)	This contraindication is applicable for all products. Hypersensitivity or anaphylactic reactions may lead to safety concern. All grades of severity are possible from mild reactions to life threatening; anaphylaxis may result in death.	No	It is common medical practice to not administer a product or any of its excipients in patients who have history of significant allergic reactions with them.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

Prolonged or cumulative exposure does not apply as Pylclari is for diagnostic use only and this medicinal product is not intended for regular or continuous administration.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Patients < 18-year-old	Patients under 18 years of age were not included in the clinical development program as prostate cancer is exceedingly rare in children and adolescents
Pregnant women	Pregnant and breastfeeding women were not included in the clinical development program as Pylclari is indicated for Positron Emission Tomography (PET) imaging in men with prostate cancer. Adults and elderly patients.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	-Patients with hepatic impairment and immunocompromised patients were not included in the clinical development program. -Patients with renal and/or cardiovascular impairment were included in this clinical development program. (1) - Immunocompromised patients and patients with a disease severity different from inclusion criteria in clinical trials were not included in the clinical development program. *Please refer to the tables below for more details.*

Population with relevant different ethnic origin	While most participants enrolled in clinical trials were White (334 patients representing 86.8% in OSPREY study and 188 patients representing 90.4% in CONDOR study), participants from other races/ethnicities were also enrolled. In the OSPREY study, 29 (7.5%) were Black or African American, 11 (2.9%) were Asian and 11 (2.9%) were another ethnicity (including not reported). In CONDOR study, 15 (7.2%) were Black or African American, 3 (1.4%) were Asian and 7 (3.4%) were another ethnicity (including not reported).
Subpopulations carrying relevant genetic polymorphisms	There is no genetic polymorphism known to have an impact on the safety and/or efficacy of Pylclari. These data where thus not collected in the clinical development program

(1) Renal impairment

An increased radiation exposure is possible in patients with reduced kidney function.

The performance of (^{18}F)-DCFPyL in patients with mild renal insufficiency was evaluated in both cohorts of men with prostate cancer in the OSPREY clinical trial (PyL 2301). No overall differences in safety or effectiveness were observed regardless of renal impairment.

Renal function was not evaluated neither in CONDOR nor in PYTHON.

Renal impairment	**OSPREY Cohort A (N=268) n (%)**	**OSPREY Cohort B (N=117) n (%)**	**Total (N=385) n (%)**
Total	264 (98.5)	116 (99.1)	380 (98.7)
eGRF 0 to <30	0	1 (0.9)	1 (0.3)
eGRF 30 to <60	16 (6.0)	13 (11.1)	29 (7.5)
eGRF 60 to <90	181 (67.5)	64 (54.7)	245 (63.6)
eGRF ≥90	67 (25.0)	38 (32.5)	105 (27.3)
Missing	4 (1.5)	1 (0.9)	5 (1.3)

eGFR = estimated glomerular filtration rate

Cardiovascular impairment

In OSPREY clinical trial (cohorts A and B), the most frequently used medications, taken by 10% or more of all patients were for cardiovascular health.

Patients with cardiovascular impairment were not assessed in PYTHON study.

Baseline medication taken by 5% or more patients, safety set	**OSPREY Cohort A (N=268) n (%)**		**OSPREY Cohort B (N=117) n (%)**	
Cardiovascular system	172 (64.2)		84 (71.8)	
ECG evaluation	Baseline	Post-dosing	Baseline	Post-dosing
Normal	159 (59.3)	155 (57.8)	55 (47.0)	51 (43.6)
Abnormal	101 (37.7)	109 (40.7)	59 (50.4)	64 (54.7)

No clinically relevant changes were observed in vital signs or ECGs from pre-dosing to post-dosing of study drug.

Part II: Module SV - Post-authorisation experience

(^{18}F)-DCFPyL Injection is only marketed in the US. On 26 May 2021, the commercially available product PYLARIFY® (piflufolastat (^{18}F)) Injection was approved by the US FDA, on the basis of multi-site registration trials (CONDOR and OSPREY), for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy.
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

PSMA PET imaging is currently **included in guidelines** for use in men with biochemical recurrence (BCR) (Mottet et al., 2021).

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The calculation of patient exposure is based on assumption that one vial is one patient.

PYLARIFY® (piflufolastat(^{18}F*)) Injection is manufactured in a multiple-dose vial containing 37 MBq/mL to 2,960 MBq/mL of piflufolastat* (^{18}F) *at calibration date and time. Imaging centers order individual patient doses from PET pharmacies. If they have multiple patients scheduled for a particular date, they order multiple single doses for those patients. In order to estimate patient exposure, it is assumed that 1 vial ordered is equivalent to 1 patient exposure. This method is a reasonable, but imperfect approximation of the use in relation to actual use/exposure, as vials may be distributed but not administered due to various reasons including product expiration dates. The dose administered to each patient is not available from distribution data.*

SV.1.2 Exposure

As of 17 November 2022, (^{18}F)-DCFPyL Injection is only marketed in the US. PYLARIFY® (piflufolastat (^{18}F)) Injection was approved by the US FDA on 26 May 2021.

98,533 patients were exposed to (^{18}F)-DCFPyL Injection until 17Nov2022 (PYLARIFY® (piflufolastat (^{18}F)) Injection) based on assumption that one vial is one patient.

Table SV.1: Exposure table by indication

Indication	Sex		Age (years)			Dose (MBq)			Formulation		Region (%)		
	Male	Female	< 65	>65	unknown	<330	>330	Unknown	Intravenous	Oral	EU country	Non EU country	Other
Scintigraphic image	X				X			X	X			100% (US)	

On the other hand, in the frame of a compassionate use program in Europe, 7,890 patients were cumulatively exposed to (^{18}F)-DCFPyL until 17Nov20222.

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable.

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Known risks that require no further characterization and are followed up via routine pharmacovigilance activities namely through signal detection and adverse reaction reporting and for which the risk minimization messages in the product information are adhered by prescribers (e.g actions being part of standard clinical practice).

Risks	Supportive information
Hypersensitivity reactions to the active substance or to any of the excipients	**Sufficiently covered by guidance in product information** Hypersensitivity may as result in wide range of reaction from mild to severe or life–threatening reaction (including anaphylactic and anaphylactoid reactions). Risk groups are patients with history of known allergies, atopic background, asthma etc. Health professionals are already aware of the risk of anaphylactic reactions and have the appropriate measures in place as part of clinical practice. These measures are also outlined in the SmPC. Hypersensitivity to the active substance or one of the excipients is included as a contraindication in section 4.3 of the SmPC. Safety measures are outlined in the section 4.4 of the SmPC: Potential for hypersensitivity or anaphylactic reactions If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available Section 4.8: Immune system disorders: Hypersensitivity Frequency: Uncommon (<1/1,000 to <1/100) Skin and subcutaneous tissue disorders: Rash Frequency: Uncommon (<1/1,000 to <1/100) General disorders and administration site conditions: Application site rash Frequency: Uncommon (<1/1,000 to <1/100) Hypersensitivity is not preventable by usual means. Prior to administration, patients should be asked about their allergy history, medical histories, and current medications. Re-exposure to the drug is at risk of a recurrent reaction.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated.

Carcinogenicity and hereditary defects due to radiation exposure	**Sufficiently covered by guidance in product information** Although radiation exposure carries an increased risk of cancer development and hereditary defects in exposed patients, the risk from medical imaging is estimated to be small (ICRP, 2007, 2001; Sodickson et al., 2009; Stabin, 2017). The benefits of medical imaging, when they are appropriate, far outweigh any radiation-associated cancer risks, and the risk from a single CT scan or nuclear imaging test is very small. The mean effective dose to the whole body from 330 MBq (^{18}F)-DCFPyL is 3.9 mSv. Increasingly, PET is now being carried out in conjunction with a low radiation dose, non-contrast CT scan for attenuation correction and anatomic localization of lesions (PET/CT). Combined PET/CT involves use of a combined full-ring detector PET scanner with a multidetector helical CT, allowing the PET scan to be acquired immediately after the CT scan. The images are then fused to give precise localization of PSMA-avid lesions. The estimated median effective dose by low dose (nondiagnostic) CT examination is 5 mSv Median total effective dose by whole body (^{18}F)-DCFPyL plus low dose nondiagnostic CT study is less than 9 mSv. As (^{18}F)-DCFPyL is a peptide no lasting deposits in the body are expected. As the mean effective dose from a PET/CT is less than the dose delivered by the association of diagnostic CT and whole-body bone scan, repetition of piflufolastat (^{18}F) PET/CT is not considered as an issue. This is a known risk that requires no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers. Safety measures are outlined in the section 4.4, 4.8, 6.6 and 12 of SmPC. Section 4.4 *Individual benefit/risk justification* For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should, in every case, be as low as reasonably achievable to obtain the required diagnostic information. *After the procedure* Close contact with infants and pregnant women should be restricted during the initial 12 hours following the injection. Section 4.8 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. Section 6.6 *General warning* 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. 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 spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken. For patients with renal failure (PSMA being mainly excreted renally): An increased radiation is possible in patients with renal impairment because approximately 50 % of the injected radioactivity is excreted in the urine around 8 hours after injection. Section 4.2 *Renal impairment* Piflufolastat (^{18}F) has only been studied in patients with mild renal impairment. Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients. Section 4.4 *Renal impairment* Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important potential Risks	Supportive information
PET imaging interpretation errors (False negative investigation result, False positive investigation result)	Reasons of classification as an important potential risk: Although the rate of inaccurate interpretation of (^{18}F)-DCFPYL PET scans in the clinical studies was found to be low, there is a potential risk that the physicians could misinterpret the images. Interpretation errors may lead to subsequent inappropriate treatment strategies for patients. ✓ Risk frequency: unknow ✓ Risk seriousness: non-serious, outcome: unknow ✓ Risk severity: Incorrect image interpretations can have severe consequences for the patient and can pose a threat to the patient's wellbeing. Impact on the benefit/risk balance: Delayed diagnosis. In the case of a false negative image interpretation, the patient may be denied a subsequent relevant treatment or may receive an inappropriate treatment, and in the case of a false positive image interpretation, the patient may be denied a curative-intent treatment or may unnecessarily be exposed to a PSMA-based therapeutic agent or other systemic treatments of prostate cancer with corresponding associated risks.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable as this is the first Risk Management Plan for Pylclari.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Potential Risk 1: PET imaging interpretation errors (False negative investigation result, False positive investigation result)	
Potential mechanisms	There is rapid distribution following intravenous administration and within 60 minutes (^{18}F)-DCFPyL distributes to the kidneys (16.5% of administered activity), liver (9.3%), and lungs

Potential Risk 1: PET imaging interpretation errors (False negative investigation result, False positive investigation result)	
	(2.9%). Most of the remaining 70% of activity at 60 minutes is with the rest of the body background region. Piflufolastat (^{18}F) accumulates in normal tissue where the density of PSMA is high including the lacrimal glands, salivary glands, liver, spleen, and kidneys (Li et al. 2017). Normal organs demonstrate significant variability in the uptake of (^{18}F)-DCFPyL; however, the impact of tumor burden on normal uptake is minimal and unlikely to be clinically significant (Sahakyan et al. 2020; Werner, Bundschuh, et al. 2020). The expression of PSMA can predominantly be found in PCa, but other benign and malignant tissues are known to express PSMA and have extensively been described: renal cell carcinoma, hepatocarcinoma, breast cancer, lung cancer and other malignancies.
Evidence source and strength of evidence	Post-marketing Spontaneous reports on the global safety database Published studies in the scientific and medical literature
Characterisation of risk	Incorrect image interpretations can have severe consequences for the patient and can pose a threat to the patient's wellbeing. In the case of a false negative image interpretation, the patient may be denied a subsequent relevant treatment or receive an inappropriate treatment, and in the case of a false positive image interpretation, the patient may be denied a curative-intent treatment or may unnecessarily be exposed to a PSMA-based therapeutic agent or other systemic treatments of prostate cancer with corresponding associated risks. Wrong diagnoses or misinterpretations of PET images are considered to be a risk linked to lack of familiarity or of complete training by image interpreters.
Risk groups or risk factors	Patient risk-factors: 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. hemangioma, renal cell carcinoma, hepatocarcinoma, breast cancer, lung cancer and other malignancies). <u>Non-patient risk factors:</u> There are no patient-specific risk groups or risk factors.
Preventability	**<u>Routine risk minimisation measures:</u>** Included as warning in SmPC sections 4.2 (image acquisition),4.4 (interpretation of images) and 5.1 (Performance of piflufolastat (^{18}F) PET/CT in studies) **<u>Additional risk minimisation measures:</u>** Provision of a self-training
Impact on the risk-benefit balance of the product	Patient diagnosis do not depend only on (^{18}F)-DCFPYL imaging. However, the risk of PET misdiagnosis may result in a delayed diagnosis, lead to the exposure of an incorrect treatment with

Potential Risk 1: PET imaging interpretation errors (False negative investigation result, False positive investigation result)	
	its related risks or to a delayed exposure to the appropriate one and may impact on patient management.
Public health impact	The public health impact is considered low.
MedDRA terms (25.1)	False positive investigation result, False negative investigation result. (PT)

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	PET imaging interpretation errors (false negative investigation result and false positive investigation results)
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted.

Specific adverse reaction follow-up questionnaires for safety concerns: N/A

Other forms of routine pharmacovigilance activities for safety concerns: N/A

III.2 Additional pharmacovigilance activities

PASS:

Study: An observational study to evaluate the effectiveness of the training program to the nuclear physicians who will have to interpret PET scans with (^{18}F)-DCFPYL CURIUM.

Rationale and study objectives:

The purpose of this PASS is to evaluate the efficacy of the training program (additional risk minimization measure).

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.

Study design:

This post-authorisation safety study (PASS) will consist of an observational study.

Study population:

Nuclear physicians from selected EU countries qualified to interpret Pylclari PET scans.

Milestones: Submission of study protocol: Q1 2024

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.3.1: 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 authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Observational study to evaluate Physician Training Methods to Read (^{18}F)-DCFPyL-PET 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 (^{18}F)-DCFPYL training programme to prevent PET imaging interpretation errors (False negative investigation result, False positive investigation result)*	*Submission of study protocol*	*Q1 2024*

Part IV: Plans for post-authorisation efficacy studies

Not applicable as no post-authorisation efficacy studies are planned.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
PET imaging interpretation errors (False positive investigation result, false	**Routine risk communication:** SmPC sections 4.2, 4.4, 5.1. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Interpretation of Pylclari PET scans with clinical correlation, which may include

negative investigation result) (potential risk)	histopathological evaluation of the suspected prostate cancer site, is recommended. **Routine risk activity:** To routinely collect and document confirmed cases of PET imaging interpretation errors (false positive and false negative diagnostic results.) **Other routine risk minimization measures beyond the product information:** None

V.2. Additional Risk Minimisation Measures

Additional risk minimisation measure: Educational material for Healthcare Professionals

Objective:

Physicians reading the scans must be specifically trained in interpreting the images from PET scans with (^{18}F)-DCFPYL, to avoid incorrect interpretation of images, which may lead to subsequent inappropriate patient management. The aim is to minimise the risks of occurrence of false positive and false, negative interpretation.

Rationale for the additional risk minimisation activity:

Routine risk minimization activities (SmPC and PIL) being not sufficient for PET imaging interpretation errors (important potential risk), including false positive and false negative results, a self-training program to nuclear physicians qualified to interpret PET scans is proposed to reduce the potential risk of PET imaging interpretation errors.

The educational material provides nuclear physicians with detailed information in order to reduce the potential risk of incorrect interpretation of (^{18}F)-DCFPYL PET scans and is prepared in collaboration with external nuclear medicine physicians with experience in the field and specifically on (^{18}F)-DCFPyL.

Target audience and planned distribution path:

The self-training program is addressed online to Nuclear Medicine specialist using (^{18}F)-DCFPYL, so that it is readily available to the health professional who will carry out the PET imaging procedure with (^{18}F)-DCFPYL in the nuclear medicine facility.

Plans to evaluate the effectiveness of the interventions and criteria for success:

A PASS is planned to:

- Evaluate the effectiveness of the educational material
- 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.

Submission of the study protocol: Q1 2024.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures	Pharmacovigilance activities
PET imaging interpretation errors (false negative and false positive)	SmPC sections 4.2, 4.4 and 5.1	Healthcare Professional self-training material: Educational materials of nuclear physicians qualified to interpret (^{18}F)-DCFPYL PET scans	PASS - To assess the effectiveness of the educational materials (Healthcare Professional self-training material).

Part VI: Summary of the risk management plan

Summary of risk management plan for Pylclari

This is a summary of the RMP for Pylclari. The RMP details important risks of Pylclari, how these risks can be minimized, and how more information will be obtained about Pylclari 's risks and uncertainties (missing information).

Pylclari 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Pylclari should be used.

This summary of the RMP for Pylclarishould be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Pylclari 's RMP.

I. The medicine and what it is used for

Pylclari is authorised 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..

It contains piflufolastat (^{18}F) as the active substance and it is given by intravenous route.

Further information about the evaluation of Pylclari's benefits can be found in Pylclari's EPAR, including its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Pylclari, together with measures to minimise such risks and the proposed studies for learning more about Pylclari 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Pylclari, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Pylclari is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Pylclari are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Pylclari. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table II.A: List of important risks and missing information

List of important risks and missing information	
Important identified risks	None
Important potential risks	PET imaging interpretation errors (False negative investigation result, False positive investigation result)
Missing information	None

II.B Summary of important risks

Table II.B: Important risks and missing information are summarised below:

Important Potential Risk - PET imaging interpretation errors (False negative investigation result, False positive investigation result)	
Evidence for linking the risk to the medicine	Post-marketing Spontaneous reports on the global safety database Published studies in the scientific and medical literature
Risk groups or risk factors	There are no patient-specific risk groups or risk factors.
Risk minimisation measures	**Routine risk minimisation measures:** Included as warning in SmPC sections 4.2 (image acquisition) 4.4 (interpretation of images) and 5.1 (Performance of piflufolastat (^{18}F) PET/CT in studies)

Important Potential Risk - PET imaging interpretation errors (False negative investigation result, False positive investigation result)	
	<u>Additional risk minimisation measures:</u> Provision of a self-training programme containing the following information: • Physiological distribution of (^{18}F)-DCFPYL. • Image interpretation guidelines. • Examples of incidental findings on PET-CT with (^{18}F)-DCFPYL. • Examples of positive and negative findings on PET-CT with (^{18}F)-DCFPYL • Self-assessment with demonstration cases about image interpretation with (^{18}F)-DCFPYL.
Additional PV activities	PASS - To assess the effectiveness of the educational materials. (Healthcare Professional self-training material)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of (^{18}F)-DCFPyL CURIUM.

II.C.2 Other studies in post-authorisation development plan

Table II.C.2 Other studies in the post-authorization development plan:

Study short name	**Rationale and study objectives**
An observational study to evaluate the effectiveness of the training program to the nuclear physicians who will have to interpret PET scans with Pylclari.	The purpose of this PASS is to evaluate the efficacy of the training program (additional risk minimization measure). 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.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Prior to the launch of Pylclari in each member state the MAH must agree about the content and the format of the self-training program, including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authority.

The self-training program is aimed to reduce the potential risk of PET imaging interpretation errors.

The MAH shall ensure that in each Member State where (Pylclari is marketed, the nuclear medicine physicians qualified to interpret PET scans in their country who are expected to use (^{18}F)-DCFPYL CURIUM have access to the self-training educational material.

The educational training material contains the following key elements:

- Physiological distribution of (^{18}F)-DCFPYL.
- Image interpretation guidelines.
- Examples of incidental findings on PET-CT with (^{18}F)-DCFPYL.
- Examples of positive and negative findings on PET-CT with (^{18}F)-DCFPYL
- Self-assessment with demonstration cases about image interpretation with (^{18}F)-DCFPYL.