2 SYNOPSIS

<table>
<tr><td>Name of Sponsor:
Theragnostics Ltd</td><td rowspan="3">Individual study table referring to part of the dossier

Volume:

Page:</td><td rowspan="3">(For national authority use only)</td></tr>
<tr><td>Name of finished product:
^{68}Ga-THP-PSMA</td></tr>
<tr><td>Name of active ingredient:
^{68}Ga-THP-PSMA
Proprietary name: Galliprost®</td></tr>
<tr><td colspan="3">Title of the study:
A Phase II, Open-Label Study to Assess Safety and Clinical Utility of ^{68}Ga-THP-PSMA PET/CT in Patients with High-Risk Primary Prostate Cancer or Biochemical Recurrence After Radical Treatment</td></tr>
<tr><td colspan="3">Investigators and study centres:
This was a single-centre study conducted at one site in the United Kingdom:

Principal Investigator: Dr Asim Afaq
Institute of Nuclear Medicine
London, UK</td></tr>
<tr><td colspan="3">Publications (references):
None</td></tr>
<tr><td colspan="2">Study period (years): 1 year
First patient on-study date: 25 June 2018
Study completion date: 12 June 2019</td><td>Clinical phase:
Phase II</td></tr>
<tr><td colspan="3">Objectives:
The primary objective of the study was:

• To evaluate gallium 68-trishydroxypyridinone-prostate-specific membrane antigen (^{68}Ga-THP-PSMA) positron emission tomography/computed tomography (PET/CT) impact on the management of patients with prostate cancer (PCa) in the setting of:
  ○ Biochemical recurrence (BCR) in patients treated with prior radical prostatectomy (RP)
  ○ BCR in patients treated with prior radiotherapy
  ○ Newly diagnosed high-risk PCa

The secondary objective of the study was:

• To evaluate the safety of ^{68}Ga-PSMA in patients with PCa.</td></tr>
<tr><td colspan="3">Methodology:
This was an open-label, single-centre study of ^{68}Ga-THP-PSMA PET/CT imaging in patients with high-risk primary PCa or BCR after radical treatment.

A single interim analysis was planned to be performed to provide some early indication of the study results and consider the primary endpoint, patient background (demographics, inclusion/exclusion criteria, prior cancer treatment, disease history and imaging history) and management (intended, revised and agreed plans).The results would not affect the planned conduct of the study, the total sample size or the planned analysis methods.</td></tr>
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The analysis was to be triggered when a pre-specified number of patients had completed their final visit (Visit 4) and the following two criteria were met:

- 30 of the 60 patients from all groups combined had completed the study.
- 10 of the 20 patients from Group B had completed the study.

However, no formal interim analysis was performed.

Number of patients (planned and analysed):

It was anticipated that 60 patients would be entered into the study, with three groups of 20 patients being studied. Group A would consist of patients with newly diagnosed primary high-risk PCa who were scheduled for RP surgery, Group B would consist of patients with a diagnosis of BCR who had previously undergone RP and were being considered for radical salvage therapy, and Group C would consist of patients with a diagnosis of BCR who had previously undergone radical radiotherapy and were being considered for radical salvage therapy.

This study enrolled 51 male patients with PCa at one site in the UK. 49 patients underwent the ^{68}Ga-THP-PSMA PET/CT scan: 20 patients in Group A, 21 patients in Group B and 8 patients in Group C.

Inclusion criteria:

Patients in Group A were required to meet all of the following criteria for inclusion in the study:

- Male patient aged ≥18 years.
- Histologically proven adenocarcinoma of the prostate gland.
- Gleason score 4+3 and above, or PSA >20 ng/mL or clinical stage >T2c.
- Suitable for surgical treatment as part of the patient's standard of care management.
- Able and willing to comply with study procedures and provide signature and date for the informed consent form (ICF) prior to any study related procedure being performed.
- Had normal or clinically acceptable medical history and vital signs findings at screening (up to four weeks before administration of ^{68}Ga-THP-PSMA).
- Had not received hormone therapy related to PCa within the past three months (other types of hormone therapy were not excluded).
- Eastern Oncology Group (ECOG) performance status of 0 to 2.

Patients in Group B were required to meet all of the following criteria for inclusion in the study:

- Male patient aged ≥18 years.
- Had had an original diagnosis of PCa, had undergone radical curative therapy at least three months prior to enrolment, and had been diagnosed with BCR based on:
  - Post RP: Two consecutive rises in prostate-specific antigen (PSA) with a three-month interval in between reads and final PSA >0.1 ng/mL **or** PSA level 0.5 mg/mL at time of recruitment. The PSA doubling time would be calculated using the Memorial Sloan Kettering Cancer Center nomogram based on a minimum of 2 PSA levels within 12 months of screening, taken after the last recorded nadir PSA available at time of screening.
- Had not had previous recurrences of PCa, i.e. this was the first diagnosis of BCR.
- Was being considered for radical salvage therapy.

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- Able and willing to comply with study procedures and provide signature and date for the ICF prior to any study related procedure being performed.
- ECOG performance status of 0 to 2.
- Had not received androgen-deprivation therapy within three months of screening.
- Had normal or clinically acceptable medical history and vital signs findings at screening (up to 14 days before administration of ^{68}Ga-THP-PSMA).
- Had not received hormone therapy related to PCa within the past three months (other types of hormone therapy were not excluded).

Patients in Group C were required to meet all of the following criteria for inclusion in the study:

- Male patient aged ≥18 years.
- Had had an original diagnosis of PCa, had undergone radical curative therapy at least three months prior to enrolment, and had been diagnosed with BCR based on:
- Increase in PSA level ~2.0 ng/mL above the nadir level after radiotherapy or brachytherapy.
- Had not had previous recurrences of PCa, i.e. this was the first diagnosis of BCR.
- Was being considered for radical salvage therapy.
- Able and willing to comply with study procedures and provide signature and date for the ICF prior to any study related procedure being performed.
- ECOG performance status of 0 to 2.
- Had not received androgen-deprivation therapy within three months of screening.
- Had normal or clinically acceptable medical history and vital signs findings at screening (up to 14 days before administration of ^{68}Ga-THP-PSMA).
- Had not received hormone therapy related to PCa within the past three months (other types of hormone therapy were not excluded).

Exclusion criteria:

Patients in Group A who met any of the following criteria were excluded from the study:

- Had received any prior treatment for prostate gland tumours.
- Had received, or were scheduled to receive, another investigational medicinal product (IMP) from one month before, to one week after, administration of ^{68}Ga-THP-PSMA injection.
- Had known hypersensitivity to ^{68}Ga-THP-PSMA injection or any of its constituents.
- Had previously been included in this study.
- Had estimated glomerular filtration rate <20 mL/min per 1.73 m^2 as assessed by local practices.

Patients in Groups B and C who met any of the following criteria were excluded from the study:

- Had previously been included in this study.
- Had received, or were scheduled to receive, another IMP from one month before, to one week after, administration of ^{68}Ga-THP-PSMA injection.
- Had known hypersensitivity to ^{68}Ga-THP-PSMA injection or any of its constituents.
- Had received hormone therapy within the past three months.
- Had estimated glomerular filtration rate <20 mL/min per 1.73 m^2 as assessed by local practices.

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Test product, dose and mode of administration, batch number:

Investigational Medicinal Product

^{68}Ga-THP-PSMA was provided by Theragnostics Ltd as a sterile solution for injection, 160±30 megabecquerels (MBq), at the reference date and time in a vial from the Good Manufacturing Practice (GMP)-validated manufacturing facility. Each vial was supplied in a container providing appropriate radiation shielding. The ^{68}Ga-THP-PSMA injection was to be kept in a locked, restricted access area when not in use and was stored at 15-25^{o}C in a shielded container and in accordance with national regulations for radioactive materials.

Batch Number

A single batch of ^{68}Ga-THP-PSMA, batch number IMP146, was used throughout the study.

Route of Administration

Prior to PET/CT, ^{68}Ga-THP-PSMA was administered in a single intravenous bolus. The administration was by a slow push over a period of 1 minute, followed by a 10 mL saline flush. ^{68}Ga-THP-PSMA was injected via a cannula with the patient lying in a supine position and in an antecubital vein (or another vein that could provide access). Any doses outside of this range were not considered a protocol violation provided that the Investigator considered the resulting scans to be of diagnostic quality.

Each individual drawn patient dose was only to be administered to the patient assigned to it. No patient was to receive more than 5 mL of the undiluted product.

Duration of treatment:

Patients were screened at Visit 1, which was carried out up to a maximum of 4 weeks before the scan date. Eligible patients received ^{68}Ga-THP-PSMA injection prior to the PET/CT scan on Visit 2 (day of scan). Patients were followed up via telephone consultation the next working day after ^{68}Ga-THP-PSMA PET/CT (Visit 3). Visit 4 (follow-up) was conducted up to 6 weeks post scan.

Criteria for evaluation:

Clinical Utility

The primary endpoint was the percentage of patients who had a change in management plan as a result of ^{68}Ga-THP-PSMA PET/CT documented after scan, compared with pre-scan management plan.

In order to derive the primary endpoint, a binary endpoint was created. A change status of 'Yes' was assigned if there was any difference in treatment options between the intended and the revised management plans. A change status of 'No' was assigned if the intended and revised management plans remained identical.

The change in management plan rate (CMPR) was calculated as the proportion of patients with a change status of 'Yes', taking as a denominator the number of patients in the analysis set. The primary analysis of CMPR was based on the Full Analysis Set (patients with all baseline study measures recorded [excluding blood pressure] who underwent the ^{68}Ga-THP-PSMA PET/CT scan, regardless

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of whether the scan was a technical success or failure). However, as a sensitivity analysis, the CMPR was also presented for the Per Protocol Analysis Set (a subset of patients from the Full Analysis Set who had a technically successful post-baseline ^{68}Ga-THP-PSMA PET/CT scan).

Safety:

Patients were assessed for safety at screening, as well as during the study and at the follow-up visit. Adverse events (AEs) regardless of suspected relationship to study treatment were recorded throughout the study, from the ^{68}Ga-THP-PSMA administration until 30 days after the administration of ^{68}Ga-THP-PSMA. All AEs were followed up until resolution or until Visit 4.

Any related SAEs that occurred at any time following 30 days after the administration of ^{68}Ga-THP-PSMA were reported.

Safety was assessed by means of physical examination, vital signs, cardiovascular profile, performance status, laboratory evaluations (haematology, biochemistry, urinalysis and PSA), recording of concurrent illness/therapy and AEs.

No dose limiting toxicity was defined in this study.

Statistical methods:

Continuous data were summarised in terms of the mean, standard deviation, median, minimum, maximum and number of observations, unless otherwise stated.

Categorical data was summarised in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages.

The study recruited three distinct patient groups (Groups A, B and C), and unless stated otherwise, the following reporting conventions applied:

Data was presented for Group A (Newly Diagnosed patients), Groups B + C (BCR Patients) and Overall (Groups A + B + C).

The sample size was based on the degree of uncertainty in the estimation of the primary outcome, the percentage of patients with a change in management, as measured by the confidence interval. Due to the phase of the study, relatively wide confidence intervals were allowed.

For Group A, previous literature suggested that approximately 25% of patients would change management. Assuming a 95% confidence level, it was calculated that 20 patients would be sufficient to obtain an estimate of the primary outcome that was within ±20% of the population value.

For Groups B+C, previous literature suggested that approximately 45% would change management. With a 95% confidence level, a sample size of 40 patients in the two groups combined would be sufficient to obtain an estimate the primary outcome that was within ±15% of the population value.

Summary conclusions:

Demographics summary:

A total of 51 male patients were enrolled and 49 patients were treated in the study. One patient failed screening as they did not meet all of the eligibility criteria and one patient was successfully enrolled but subsequently withdrew their consent prior to receiving ^{68}Ga-THP-PSMA. Overall, 20 patients were treated in Group A, 21 patients in Group B and 8 patients in Group C, comprising the safety evaluable population.

The median age of all patients was 67.0 years (range: 43-80 years). Thirty-four patients (69.4%) were white, 12 patients (24.5%) were black and three patients (6.1%) were Asian. At the time of enrolment, 48 patients (98.0%) had an ECOG performance status of 0 and one patient (2.0%) had an ECOG performance status of 1.

Safety summary:

Forty-nine patients received ^{68}Ga-THP-PSMA and were evaluated for safety. ^{68}Ga-THP-PSMA was well tolerated. No patients experienced SAEs, discontinued the study due to AEs, or died during the study. Eleven AEs were reported by a total of five patients (10.2%) during the study, all of which were treatment emergent AEs (TEAEs). The system organ class with the highest proportion of patients reporting at least one TEAE was nervous system disorders (four TEAEs in three patients). The most common TEAE was syncope (two TEAEs in one patient). Two drug-related TEAEs were reported (one event of pruritus in one patient and one event of catheter site rash in one patient). The highest grade TEAEs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 3, experienced by two patients. One patient experienced two CTCAE Grade 3 TEAEs of syncope and one patient experienced on CTCAE Grade 3 TEAE of palpitations. None of the Grade 3 events were considered related to ^{68}Ga-THP-PSMA.

Clinical utility summary:

The primary objective of this trial was to evaluate the impact of ^{68}Ga-THP-PSMA PET/CT on the management of patients with PCa. This was analysed by measuring the percentage of patients who had a change in management plan as a result of ^{68}Ga-THP-PSMA PET/CT documented after scan, compared with their pre-scan management plan. This was assessed in the full analysis set (all patients who underwent a ^{68}Ga-THP-PSMA PET/CT, regardless of whether the scan was a technical success or failure), but was also assessed in the per protocol population (all patients who underwent at least one technically successful ^{68}Ga-THP-PSMA PET/CT), in case there was a difference between the two. All 49 patients (100.0%) who received ^{68}Ga-THP-PSMA in this study underwent at least one technically successful post-baseline ^{68}Ga-THP-PSMA PET/CT so were included in both the full analysis and per protocol populations.

Overall, 21 patients had a change in management plan as a result of the ^{68}Ga-THP-PSMA PET/CT scan; six patients (30.0%) in Group A and 15 patients (51.7%) in Groups B+C. The results from this study are consistent with previous literature [19, 20, 21, 22] which suggested that 25% of patients in Group A and 45% of patients in Groups B+C would change management plan as a result of the ^{68}Ga-THP-PSMA PET/CT scan.

The technical feasibility of ^{68}Ga-THP-PSMA PET/CT was an exploratory objective of the study and was evaluated by assessing the technical success/failure of the scans, the presence or absence of imaging artefacts and difficulties in interpretation of the scan. All 49 patients (100.0%) had a technically successful scan. The scans from two patients were not optimal (imaging artefacts were identified in both scans and one was also difficult to interpret), however, they were still of diagnostic quality.

The other tertiary objective (to assess the correlation of PSMA on imaging and PSMA within tumour), was not evaluated during the study.

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Overall conclusions:

^{68}Ga-THP-PSMA was administered to 20 patients with newly diagnosed PCa (Group A) and 29 patients with BCR (Groups B+C). All 49 patients (100.0%) were evaluated for the primary objective of the study, to assess the impact of ^{68}Ga-THP-PSMA PET/CT on the management of patients with PCa. A total of 21 patients changed management plan as a result of ^{68}Ga-THP-PSMA PET/CT; six patients (30.0%) in Group A and 15 patients (51.7%) in Groups B+C. These results were consistent with previous literature which suggested that 25% of patient in Group A and 45% of patient in Groups B+C would change management plans as a result of the ^{68}Ga-THP-PSMA PET/CT scan.

The secondary objective of the study, to assess the safety of ^{68}Ga-THP-PSMA in patients with PCa, was completed. ^{68}Ga-THP-PSMA was well tolerated. No patients experienced SAEs, discontinued the study due to AEs or died during the study. A total of 11 TEAEs were reported by five patients, two of which were considered related to ^{68}Ga-THP-PSMA. The highest CTCAE Grade TEAEs were Grade 3; two patients experienced by three Grade 3 TEAEs during the study.

The technical feasibility of ^{68}Ga-THP-PSMA PET/CT was also assessed as an exploratory objective of the study. All 49 patients (100.0%) underwent a successful ^{68}Ga-THP-PSMA PET/CT scan. The scans from two patients were not optimal (due to imaging artefacts and difficulties in interpretation), however, they were still of diagnostic quality.

The final exploratory objective (to assess the correlation of PSMA on imaging and PSMA within tumour), was not evaluated during this study.