SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Pluvicto 1,000 MBq/mL solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 1,000 MBq of lutetium (^{177}Lu) vipivotide tetraxetan at the date and time of calibration.

The total amount of radioactivity per single-dose vial is 7,400 MBq at the date and time of administration. Given the fixed volumetric activity of 1,000 MBq/mL at the date and time of calibration, the volume of the solution in the vial can range from 7.5 mL to 12.5 mL in order to provide the required amount of radioactivity at the date and time of administration.

Physical characteristics

Lutetium-177 has a half-life of 6.647 days. Lutetium-177 decays by β^- emission to stable hafnium-177 with the most abundant β^- (79.3%) having a maximum energy of 0.497 MeV. The average beta energy is approximately 0.13 MeV. Low gamma energy is also emitted, for instance at 113 keV (6.2%) and 208 keV (11%).

Excipient with known effect

Each mL of solution contains up to 0.312 mmol (7.1 mg) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless to slightly yellow solution.

pH: 4.5 to 7.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pluvicto is indicated for the treatment of adult patients with

- prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have progressed on or after treatment with androgen receptor pathway inhibitor (ARPI) therapy and are considered appropriate to delay taxane-based chemotherapy.

- prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes.

4.2 Posology and method of administration

Important safety instructions

Pluvicto should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section 6.6) and after evaluation of the patient by a qualified physician.

Radiopharmaceuticals, including Pluvicto, should be used by or under the control of healthcare professionals who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorised to license the use of radiopharmaceuticals.

Pluvicto is a radiopharmaceutical and should be handled with appropriate safety measures to minimise radiation exposure (see section 4.4). Waterproof gloves and effective radiation shielding should be used when handling Pluvicto.

Patient identification

Patients should be identified for treatment by PSMA imaging.

Posology

The recommended Pluvicto dose is 7,400 MBq intravenously every 6 weeks (±1 week) for a total of 6 doses.

Treatment monitoring
Laboratory tests should be performed before and during treatment with Pluvicto.

- Haematology (haemoglobin, white blood cell count, absolute neutrophil count, platelet count)
- Kidney function (serum creatinine, calculated creatinine clearance [CLcr])

- Liver function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood serum albumin, total blood bilirubin)

Dose modifications for adverse drug reactions (ADRs)
Recommended dose modifications of Pluvicto for ADRs are provided in Table 1. Management of severe or intolerable ADRs may require temporary dose interruption, dose reduction or permanent discontinuation of treatment with Pluvicto. If a treatment delay due to an adverse drug reaction persists for > 4 weeks, treatment with Pluvicto must be discontinued. The dose of Pluvicto may be reduced by 20% to 5 900 MBq once; the dose should not be re-escalated. If a patient has further adverse drug reactions that would require an additional dose reduction, treatment with Pluvicto must be discontinued.

Table 1 Recommended dose modifications of Pluvicto for ADRs

ADR	**Severity[a]**	**Dose modification**
Dry mouth	Grade ≥3	Reduce Pluvicto dose by 20% to 5 900 MBq.
Gastrointestinal toxicity	Grade ≥3 (not amenable to medical intervention)	Withhold Pluvicto until improvement to grade 2 or baseline. Reduce Pluvicto dose by 20% to 5 900 MBq.
Myelosuppresion (anaemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia)	Grade 2	Withhold Pluvicto until improvement to grade 1 or baseline. Manage as deemed appropriate. The use of growth factors is permitted but should be discontinued once improved to grade 1 or baseline. Checking haematinic levels (iron, B12 and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated.
	Grade ≥3	Withhold Pluvicto until improvement to Grade 1 or baseline. Reduce Pluvicto dose by 20% to 5 900 MBq.
Renal toxicity	Defined as: • Confirmed serum creatinine increase (grade ≥2) • Confirmed CLcr < 30 mL/min; calculate using Cockcroft-Gault with actual body weight	Withhold Pluvicto until improvement.

	Defined as: • Confirmed ≥40% increase from baseline serum creatinine and • Confirmed >40% decrease from baseline CLcr; calculate using Cockcroft-Gault with actual body weight	Withhold Pluvicto until improvement or return to baseline. Reduce Pluvicto dose by 20% to 5 900 MBq.
	Recurrent renal toxicity (grade ≥3)	Permanently discontinue Pluvicto.
Spinal cord compression	Any	Withhold Pluvicto until the compression has been adequately treated and any neurological sequela have stabilised and ECOG performance status has stabilised.
Fracture in weight-bearing bones	Any	Withhold Pluvicto until the fracture has been adequately stabilised/treated and ECOG performance status has stabilised.
AST or ALT elevation	AST or ALT >20 times ULN in the absence of liver metastases	Permanently discontinue Pluvicto.
Abbreviations: CLcr, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal. Grading according to most current Common Terminology Criteria for Adverse Events (CTCAE). [a] The same thresholds are also applicable to baseline values at the time of treatment initiation with Pluvicto.		

Special populations

Elderly

No dose adjustment is recommended in patients aged 65 years or older (see section 5.2).

Renal impairment

No dose adjustment is recommended for patients with mild (baseline CLcr 60 to 89 mL/min by Cockcroft-Gault) to moderate (CLcr 30 to 59 mL/min) renal impairment. The pharmacokinetic profile and safety of Pluvicto have not been studied in patients with severe (CLcr 15 to 29 mL/min) renal impairment or end-stage renal disease (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is recommended for patients with hepatic impairment.

Paediatric population

There is no relevant use of Pluvicto in the paediatric population in the indication of treatment of PSMA-expressing prostate cancer.

Method of administration

Pluvicto is for intravenous use. It is a ready to use radiopharmaceutical medicinal product for single use only.

Preparation instructions

- Aseptic technique and radiation shielding should be used when handling or administering Pluvicto, using tongs as needed to minimise radiation exposure.
- The product should be visually inspected under a shielded screen for particulate matter and discoloration prior to administration. The vial should be discarded if particulates or discoloration are present.
- The Pluvicto solution should not be injected directly into any other intravenous solution.
- The amount of radioactivity delivered to the patient should be confirmed with an appropriately calibrated dose calibrator prior to and after each Pluvicto administration.

Administration instructions

The recommended dose of Pluvicto may be administered intravenously as an injection using the syringe method, as an infusion using the gravity method, or as an infusion using the peristaltic pump method.

When using the gravity or peristaltic pump method, Pluvicto should be infused directly from its original container.

The syringe method or the peristaltic pump method should be used when administering a reduced dose of Pluvicto following a dose modification for an adverse reaction. When using the gravity method for a reduced dose, the Pluvicto dose should be adjusted before the administration to avoid the delivery of an incorrect volume of Pluvicto.

Prior to administration, the intravenous catheter used exclusively for Pluvicto administration should be flushed with ≥10 mL of 0.9% sterile sodium chloride solution to ensure patency and to minimise the risk of extravasation. Cases of extravasation should be managed as per institutional guidelines.

Intravenous methods of administration

Instructions for the syringe method

- Withdraw an appropriate volume of Pluvicto solution to deliver the desired radioactivity by using a disposable syringe fitted with a syringe shield and a disposable sterile needle that is 9 cm, 18 gauge (long needle). To aid the withdrawal of the solution, a filtered 2.5 cm, 20 gauge needle (short venting needle) can be used to reduce the resistance from the pressurised vial. Ensure that the short needle does not touch the Pluvicto solution in the vial.
- If using a syringe pump, fit the syringe into the shielded pump and include a 3-way stopcock valve between the syringe and an intravenous catheter primed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection and used for Pluvicto administration to the patient.
- Administer Pluvicto to the patient by slow intravenous push within approximately 1 to 10 minutes (either with a syringe pump or manually without a syringe pump) via an intravenous catheter that is primed with 0.9% sterile

sodium chloride solution and that is used exclusively for Pluvicto administration to the patient.

- When the desired Pluvicto radioactivity has been delivered, stop the syringe pump and then change the position of the 3-way stopcock valve to flush the syringe with 25 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection. Restart the syringe pump.
- After the flush of the syringe has been completed, perform an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Instructions for the gravity method

- Insert a 2.5 cm, 20 gauge needle (short needle) into the Pluvicto vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (used to transport the Pluvicto solution during the infusion). Ensure that the short needle does not touch the Pluvicto solution in the vial and do not connect the short needle directly to the patient. Do not allow the sodium chloride solution to flow into the Pluvicto vial prior to the initiation of the Pluvicto infusion and do not inject the Pluvicto solution directly into the sodium chloride solution.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the Pluvicto vial, ensuring that the long needle touches and is secured to the bottom of the Pluvicto vial during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is primed with 0.9% sterile sodium chloride solution and that is used exclusively for the Pluvicto infusion into the patient.
- Use a clamp or an infusion pump to regulate the flow of the sodium chloride solution via the short needle into the Pluvicto vial (the sodium chloride solution entering the vial through the short needle will carry the Pluvicto solution from the vial to the patient via the intravenous catheter connected to the long needle within approximately 30 minutes).
- During the infusion, ensure that the level of solution in the Pluvicto vial remains constant.
- Disconnect the vial from the long needle line and clamp the saline line once the level of radioactivity is stable for at least five minutes.
- Follow the infusion with an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Instructions for the peristaltic pump method

- Insert a filtered 2.5 cm, 20 gauge needle (short venting needle) into the Pluvicto vial. Ensure that the short needle does not touch the Pluvicto solution in the vial and do not connect the short needle directly to the patient or to the peristaltic pump.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the Pluvicto vial, ensuring that the long needle touches and is secured to the bottom of the Pluvicto vial during the entire infusion. Connect the long needle and a 0.9% sterile sodium chloride solution to a 3-way stopcock valve via appropriate tubing.
- Connect the output of the 3-way stopcock valve to tubing installed on the input side of the peristaltic pump according to manufacturer’s instructions.
- Prime the line by opening the 3-way stopcock valve and pumping the Pluvicto solution through the tubing until it reaches the exit of the valve.

- Prime the intravenous catheter which will be connected to the patient by opening the 3-way stopcock valve to the 0.9% sterile sodium chloride solution and pumping the 0.9% sterile sodium chloride solution until it exits the end of the catheter tubing.
- Connect the primed intravenous catheter to the patient and set the 3-way stopcock valve such that the Pluvicto solution is in line with the peristaltic pump.
- Infuse an appropriate volume of Pluvicto solution at approximately 25 mL/h to deliver the desired radioactivity.
- When the desired Pluvicto radioactivity has been delivered, stop the peristaltic pump and then change the position of the 3-way stopcock valve so that the peristaltic pump is in line with the 0.9% sterile sodium chloride solution. Restart the peristaltic pump and infuse an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

For patient preparation, see section 4.4.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 therapeutic effect.

Risk from radiation exposure

Pluvicto contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

Radiation exposure to patients, medical personnel, and others should be minimised during and after treatment with Pluvicto consistent with institutional good radiation safety practices, patient management procedures, and instructions to the patient for follow-up radiation protection at home.

Patient preparation
Patients should be encouraged to increase oral fluids and urged to void as often as possible to reduce bladder radiation, especially after high activities, e.g. for radionuclide therapy.

After the procedure

Before the patient is released, the nuclear medicine physician or healthcare provider should explain the necessary radioprotection precautions that the patient should follow to minimise radiation exposure to others.

Following administration of Pluvicto, patients should be advised to:

- limit close contact (less than 1 meter) with others for 2 days or with children and pregnant women for 7 days.
- refrain from sexual activity for 7 days.
- sleep in a separate room from others for 3 days, from children for 7 days, or from pregnant women for 15 days.

Myelosuppression

In the PSMAfore study, myelosuppression occurred more frequently in patients who received Pluvicto compared to patients who switched to another ARPI therapy (see section 4.8)

In the VISION study, myelosuppression occurred more frequently in patients who received Pluvicto plus best standard of care (BSoC) compared to patients who received BSoC alone (see section 4.8).

Haematology laboratory tests, including haemoglobin, white blood cell count, absolute neutrophil count and platelet count, should be performed before and during treatment with Pluvicto. Pluvicto should be withheld, dose reduced, or permanently discontinued and patients should be clinically managed as deemed appropriate based on the severity of myelosuppression (see section 4.2).

Renal toxicity

In the PSMAfore study, renal toxicity was comparable in patients who received Pluvicto compared to patients who switched to another ARPI therapy (see section 4.8)

In the VISION study, renal toxicity occurred more frequently in patients who received Pluvicto plus BSoC compared to patients who received BSoC alone (see section 4.8).

Patients should be advised to remain well hydrated and to urinate frequently before and after administration of Pluvicto. Kidney function laboratory tests, including serum creatinine and calculated CLcr, should be performed before and during treatment with Pluvicto. Pluvicto should be withheld, dose reduced, or permanently discontinued based on the severity of renal toxicity (see section 4.2).

Renal/Hepatic impairment

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Exposure (AUC) of lutetium (^{177}Lu) vipivotide tetraxetan is expected to increase with the degree of renal impairement (see section 5.2). Patients with mild or moderate

renal impairment may be at greater risk of toxicity. Renal function and adverse drug reactions should be frequently monitored in patients with mild to moderate renal impairment (see section 4.2). The pharmacokinetic profile and safety of lutetium (^{177}Lu) vipivotide tetraxetan have not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease.

Specific warnings

Sodium content
This medicinal product contains up to 3.9 mmol (88.75 mg) sodium per dose, equivalent to 4.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies were required.

4.6 Fertility, pregnancy and lactation

Contraception in males

Based on its mechanism of action, male patients should be advised not to father a child and to use condoms for intercourse during treatment with Pluvicto and for 14 weeks after the last dose.

Pregnancy

The safety and efficacy of Pluvicto have not been established in females as Pluvicto is not indicated for use in females. No animal studies using lutetium (^{177}Lu) vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-foetal development; however, all radioactive emissions, including those from Pluvicto, can cause foetal harm. Based on its mechanism of action, Pluvicto can cause foetal harm when administered to a pregnant woman (see section 5.1).

Breast-feeding

The safety and efficacy of Pluvicto have not been established in females as Pluvicto is not indicated for use in females. There are no data on the presence of lutetium (^{177}Lu) vipivotide tetraxetan in human milk or its effects on the breast-fed newborn/infant or on milk production.

Fertility

No studies were conducted to determine the effects of lutetium (^{177}Lu) vipivotide tetraxetan on fertility. The recommended cumulative dose of 44,400 MBq of Pluvicto results in a radiation absorbed dose to the testes within the range where Pluvicto may cause infertility.

4.7 Effects on ability to drive and use machines

Pluvicto has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases it is necessary to ensure that the risks of the radiation are less than from the disease itself.

PSMAfore Study: Summary of the safety profile

The safety of Pluvicto was evaluated in the Phase III PSMAfore study in patients with progressive, PSMA-positive mCRPC previously treated with ARPI therapy. Of the 468 patients randomised, 459 patients received at least one dose of randomised treatment. Patients received either Pluvicto 7,400 MBq administered every 6 weeks (N = 227) or a change in ARPI (N = 232).

Among patients who received Pluvicto, the median number of doses of Pluvicto received was 6 (range: 1 to 6), with 63.4% of patients who received all 6 doses of Pluvicto. The median cumulative dose of Pluvicto was 42,400 MBq (range: 7,000 to 45,400). The median duration of exposure to randomised treatment was 8.4 months (range: 0.4 to 11.6) for patients who received Pluvicto and 6.5 months (range: 0.03 to 29.2) for patients who received a change in ARPI. The data analyses presented below do not include patients who crossed over to receive Pluvicto after receiving treatment in the change in ARPI arm.

Table 2 summarises the incidence of adverse drug reactions. The most common adverse drug reactions (≥20%) in patients who received Pluvicto include: dry mouth (60.8%), fatigue (52.9%), nausea (31.7%), anaemia (27.3%), constipation (22.0%) and decreased appetite (21.6%). The most common Grade 3 to 4 adverse drug reactions (≥5%) in patients who received Pluvicto include: anaemia (6.2%).

Tabulated list of ADRs

ADRs (Table 2) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each ADR is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2 Adverse drug reactions in patients who received Pluvicto compared to a change in ARPI in PSMAfore[a]

ADRs	Frequency category	All grades n (%)	Grades 3 to 4[b] n (%)
Infections and infestations			
Urinary tract infection[c]	Common	13 (5.7)	3 (1.3)
Oral fungal infection[d]	Common	7 (3.1)	0
Blood and lymphatic system disorders			
Anaemia	Very common	62 (27.3)	14 (6.2)
Leukopenia[e]	Very common	25 (11.0)	5 (2.2)
Thrombocytopenia	Very common	23 (10.1)	7 (3.1)
Lymphopenia	Common	15 (6.6)	10 (4.4)
Pancytopenia	Uncommon	1 (0.4)	0
Metabolism and nutrition disorders			
Decreased appetite	Very common	49 (21.6)	0
Nervous system disorders			
Dysgeusia[f]	Common	20 (8.8)	0
Headache	Common	19 (8.4)	0
Dizziness	Common	10 (4.4)	0
Eye disorders			
Dry eye[g]	Common	14 (6.2)	0
Ear and labyrinth disorders			
Vertigo	Common	4 (1.8)	0
Gastrointestinal disorders			
Dry mouth[h]	Very common	138 (60.8)	2 (0.9)
Nausea	Very common	72 (31.7)	0
Constipation	Very common	50 (22.0)	1 (0.4)
Diarrhoea	Very common	38 (16.7)	0
Vomiting	Very common	26 (11.5)	0
Abdominal pain[i]	Common	21 (9.3)	2 (0.9)
Oesophageal disorder[j]	Common	9 (4.0)	1 (0.4)
Stomatitis	Common	3 (1.3)	1 (0.4)
Skin and subcutaneous tissue disorders			
Dry Skin	Common	9 (4.0)	0
Renal and urinary disorders			
Acute kidney injury[l]	Common	15 (6.6)	3 (1.3)
General disorders and administration site conditions			
Fatigue[m]	Very common	120 (52.9)	3 (1.3)
Oedema peripheral	Common	19 (8.4)	0
Pyrexia	Common	6 (2.6)	1 (0.4)
Investigations			
Weight decreased	Common	15 (6.6)	1 (0.4)

Abbreviation: ARPI, androgen receptor pathway inhibitor.

*Patients in the Pluvicto arm do not include patients who crossed over to receive Pluvicto after receiving treatment in the change in ARPI arm.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

[b]Only includes Grades 3 to 4 adverse drug reactions, no grade 5 adverse drug reactions recorded during treatment phase.

[c]Urinary tract infection includes urinary tract infection, cystitis, and urinary tract infection enterococcal.

[d]Oral fungal infection includes candida infection, oral candidiasis, oral fungal infection, and oropharyngeal candidiasis.

[e]Leukopenia includes neutropenia and leukopenia.

[f]Dysgeusia includes dysgeusia and taste disorder.

[g]Dry eye includes dry eye and xerophthalmia.

[h]Dry mouth includes dry mouth, mucosal dryness, salivary hyposecretion, dry throat, and lip dry.

[i]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, and epigastric discomfort.

[j]Oesophageal disorder includes gastrooesophageal reflux disease, dysphagia, oesophagitis, and burn oesophageal.

[k]Dry skin includes xerosis and dry skin.

[l]Acute kidney injury includes blood creatinine increased, acute kidney injury, renal failure, and blood urea increased.

[m]Fatigue includes asthenia and fatigue.

Description of selected ADRs

Myelosuppression

In the PSMAfore study, myelosuppression occurred more frequently in patients who received Pluvicto compared to patients who received a change in ARPI (all Grades/Grade ≥3): anaemia (26.9%/6.2%) versus (19.0%/6.9%); thrombocytopenia (7.5%/2.2%) versus (3.0%/0.9%); neutropenia (5.7%/1.3%) versus (0.9%/0.4%); leukopenia (2.2%/0.9%) versus (0%/0%); lymphopenia (1.8%/0.4%) versus (0%/0%); and pancytopenia (0.4%/0%) versus (0.4%/0%). One fatal case of bone marrow failure occurred during the long term follow-up period in a patient treated with Pluvicto.

Myelosuppression adverse drug reactions that led to permanent discontinuation in ≥0.5% of patients who received Pluvicto included: thrombocytopenia (1.3%). Myelosuppression adverse drug reactions that led to dose interruptions /dose reductions in ≥0.5% of patients who received Pluvicto included: anaemia (1.8%/0.4%) and neutropenia (0.9%/0.4%).

Renal toxicity

In the PSMAfore study, renal toxicity was comparable in patients who received Pluvicto compared to patients who received a change in ARPI (all Grades/Grade 3 to 4): blood creatinine increased (4.4%/0%) versus (3.0%/0%); acute kidney injury (2.2%/1.3%) versus (3.9%/2.2%); renal failure (0.9%/0.4%) versus (1.3%/0.9%); and blood urea increased (0.4%/0%) versus (0%/0%).

Renal adverse drug reactions that led to permanent discontinuation in ≥0.4% of patients who received Pluvicto included: acute kidney injury (0.4%). Renal adverse drug reactions that led to dose interruptions /dose reductions in ≥0.4% of patients who received Pluvicto included: blood creatinine increased (0.4%/0%) and renal failure (0.4%/0%).

VISION Study: Summary of the safety profile

The safety of Pluvicto was evaluated in the phase III VISION study in patients with progressive, PSMA-positive mCRPC. Of the 831 patients randomised, 734 patients received at least one dose of randomised treatment. Patients received at least one dose of either

Pluvicto 7,400 MBq administered every 6 to 10 weeks plus BSoC (n=529) or BSoC alone (n=205).

Among patients who received Pluvicto plus BSoC, the median number of doses of Pluvicto received was 5 (range: 1 to 6), with 67.7% of patients who received at least 4 doses of Pluvicto and 46.5% of patients who received a total of 6 doses of Pluvicto. The median cumulative dose of Pluvicto was 37,500 MBq (range: 7,000 to 48,300). The median duration of exposure to randomised treatment was 7.8 months (range: 0.3 to 24.9) for patients who received Pluvicto plus BSoC and 2.1 months (range: 0.0 to 26.0) for patients who received BSoC alone.

Table 3 summarises the incidence of ADRs. The most common ADRs (≥20%) occurring at a higher incidence in patients who received Pluvicto plus BSoC compared to BSoC alone include: fatigue (48.0%), dry mouth (39.3%), nausea (35.7%), anaemia (31.9%), decreased appetite (21.4%) and constipation (20.2%). The most common grade 3 to 4 ADRs (≥5%) occurring at a higher incidence in patients who received Pluvicto plus BSoC compared to BSoC alone include: anaemia (12.9%), thrombocytopenia (7.9%), lymphopenia (7.8%) and fatigue (6.6%).

At the time of VISION final analysis, after a median follow-up duration of 14.2 months (range: 0.6 to 60.9 months), the overall safety profile remained consistent with that previously reported.

Tabulated list of ADRs

ADRs (Table 3) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each ADR is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 3 ADRs occurring at a higher incidence in patients who received Pluvicto plus BSoC compared to BSoC alone in VISION[a]

ADRs	Frequency category	All grades n (%)	grades 3 to 4[b] n (%)
Infections and infestations			
Oral fungal infection[c]	Common	13 (2.5)	0 (0.0)
Blood and lymphatic system disorders			
Anaemia	Very common	169 (31.9)	68 (12.9)
Thrombocytopenia	Very common	91 (17.2)	42 (7.9)
Leukopenia[d]	Very common	83 (15.7)	22 (4.2)
Lymphopenia	Very common	75 (14.2)	41 (7.8)
Pancytopenia[e]	Common	9 (1.7)	7 (1.3)[b]
Bone marrow failure	Uncommon	1 (0.2)	1 (0.2)[b]
Nervous system disorders			
Dizziness	Common	44 (8.3)	5 (0.9)
Headache	Common	37 (7.0)	4 (0.8)
Dysgeusia[f]	Common	37 (7.0)	0 (0.0)
Eye disorders			
Dry eye	Common	16 (3.0)	0 (0.0)
Ear and labyrinth disorders			
Vertigo	Common	11 (2.1)	0 (0.0)

Gastrointestinal disorders			
Dry mouth[g]	Very common	208 (39.3)	0 (0.0)
Nausea	Very common	189 (35.7)	7 (1.3)
Constipation	Very common	107 (20.2)	6 (1.1)
Vomiting[h]	Very common	101 (19.1)	5 (0.9)
Diarrhoea	Very common	101 (19.1)	4 (0.8)
Abdominal pain[i]	Very common	61 (11.5)	7 (1.3)
Oesophageal disorder[j]	Common	18 (3.4)	1 (0.2)
Stomatitis	Common	9 (1.7)	1 (0.2)
Skin and subcutaneous tissue disorders			
Dry skin[k]	Common	8 (1.5)	0 (0.0)
Renal and urinary disorders			
Urinary tract infection[l]	Very common	63 (11.9)	20 (3.8)
Acute kidney injury[m]	Common	48 (9.1)	18 (3.4)
General disorders and administration site conditions			
Fatigue[n]	Very common	254 (48.0)	35 (6.6)
Decreased appetite	Very common	113 (21.4)	10 (1.9)
Weight decreased	Very common	58 (11.0)	2 (0.4)
Oedema peripheral[o]	Common	53 (10.0)	2 (0.4)
Pyrexia	Common	37 (7.0)	2 (0.4)

Abbreviation: BSoC, best standard of care.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

[b] Only includes grades 3 to 4 ADRs, with the exception of pancytopenia and bone marrow failure. Grade 5 (fatal) pancytopenia was reported in 2 patients who received Pluvicto plus BSoC. Grade 5 (fatal) bone marrow failure was reported in 1 patient who received Pluvicto plus BSoC.

[c] Oral fungal infection includes oral candidiasis, candida infection, oral fungal infection, oropharyngitis fungal and tongue fungal infection.

[d] Leukopenia includes leukopenia and neutropenia.

[e] Pancytopenia includes pancytopenia and bicytopenia.

[f] Dysgeusia includes dysgeusia and taste disorder.

[g] Dry mouth includes dry mouth, lip dry, salivary hyposecretion and dry throat.

[h] Vomiting includes vomiting and retching.

[i] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness and gastrointestinal pain.

[j] Oesophageal disorder includes gastrooesophageal reflux disease, dysphagia and oesophagitis.

[k] Dry skin includes dry skin and xeroderma.

[l] Urinary tract infection includes urinary tract infection, cystitis and cystitis bacterial.

[m] Acute kidney injury includes blood creatinine increased, acute kidney injury, renal failure and blood urea increased.

[n] Fatigue includes fatigue and asthenia.

[o] Oedema peripheral includes oedema peripheral, fluid retention and hypervolaemia.

Description of selected ADRs

Myelosuppression

In the VISION study, myelosuppression occurred more frequently in patients who received Pluvicto plus BSoC compared to patients who received BSoC alone (all grades/grade ≥3): anaemia (31.9%/12.9%) versus (13.2%/4.9%); thrombocytopenia (17.2%/7.9%) versus (4.4%/1.0%); leukopenia (12.5%/2.5%) versus (2.0%/0.5%); lymphopenia (14.2%/7.8%)

versus (3.9%/0.5%); neutropenia (8.5%/3.4%) versus (1.5%/0.5%); pancytopenia (1.5%/1.1%) versus (0%/0%) including two fatal events of pancytopenia in patients who received Pluvicto plus BSoC; and bicytopenia (0.2%/0.2%) versus (0%/0%);and bone marrow failure (0.2%/0.2%) versus (0%/0%) including one fatal event of bone marrow failure in a patient who received Pluvicto plus BSoC.

Myelosuppression ADRs that led to permanent discontinuation in ≥0.5% of patients who received Pluvicto plus BSoC included: anaemia (2.8%), thrombocytopenia (2.8%), leukopenia (1.3%), neutropenia (0.8%) and pancytopenia (0.6%). Myelosuppression ADRs that led to dose interruptions/dose reductions in ≥0.5% of patients who received Pluvicto plus BSoC included: anaemia (5.1%/1.3%), thrombocytopenia (3.6%/1.9%), leukopenia (1.5%/0.6%) and neutropenia (0.8%/0.6%).

Renal toxicity
In the VISION study, renal toxicity occurred more frequently in patients who received Pluvicto plus BSoC compared to patients who received BSoC alone (all grades/grades 3 to 4): blood creatinine increased (5.7%/0.2%) versus (2.4%/0.5%); acute kidney injury (3.8%/3.2%) versus (3.9%/2.4%); renal failure (0.2%/0%) versus (0%/0%); and blood urea increased (0.2%/0%) versus (0%/0%).

Renal ADRs that led to permanent discontinuation in ≥0.2% of patients who received Pluvicto plus BSoC included: blood creatinine increased (0.2%). Renal ADRs that led to dose interruptions/dose reductions in ≥0.2% of patients who received Pluvicto plus BSoC included: blood creatinine increased (0.2%/0.4%) and acute kidney injury (0.2%/0%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of administration of a radiation overdose with Pluvicto, the radiation absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective radiation dose that was applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: V10XX05

Mechanism of action

The active moiety of Pluvicto is the radionuclide lutetium-177 which is linked to a targeting moiety that binds with high affinity to PSMA, a transmembrane protein that is highly expressed in prostate cancer, including mCRPC. Upon the binding of Pluvicto to PSMA-expressing cancer cells, the beta-minus emission from lutetium-177 delivers therapeutic radiation to the targeted cell, as well as to surrounding cells, and induces DNA damage which can lead to cell death.

Pharmacodynamic effects

There are no data regarding lutetium (^{177}Lu) vipivotide tetraxetan exposure-efficacy relationships and the time course of pharmacodynamic response.

There are limited data regarding lutetium (^{177}Lu) vipivotide tetraxetan exposure-safety relationships and the time course of pharmacodynamic response.

Vipivotide tetraxetan does not have any pharmacodynamic activity.

Clinical efficacy and safety

PSMAfore Study

The efficacy of Pluvicto in patients with progressive, PSMA-positive mCRPC previously treated with ARPI therapy was established in PSMAfore, a randomised, multicenter, open-label Phase III study. Four hundred and sixty-eight (N = 468) patients were randomised (1:1) to receive either Pluvicto 7,400 MBq every 6 weeks for a total of 6 doses (N = 234) or a change in ARPI (N = 234).

Patients maintained castrate levels of serum/plasma testosterone by either medical castration or prior orchiectomy. Eligible patients were required to be candidates for ARPI switch, have PSMA-positive mCRPC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1, at least one metastatic lesion present on computed tomography (CT), magnetic resonance imaging (MRI) or bone scan imaging, and adequate renal, hepatic and hematological function.

Eligible patients were also required to have progressed only once on an ARPI (abiraterone acetate, enzalutamide, darolutamide, or apalutamide). Prior taxane-based chemotherapy was only allowed in the adjuvant or neoadjuvant setting greater than 12 months before enrollment. Patients with unstable symptomatic central nervous system metastases or symptomatic or clinically/radiologically impending spinal cord compression were not eligible for the study. Patients underwent a gallium (68Ga) gozetotide positron emission tomography (PET) scan to evaluate PSMA expression in lesions defined by central read criteria. Eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumor lesion with gallium (68Ga) gozetotide uptake greater than in normal liver. Patients were considered ineligible if any intraprostatic lesion or any one lesion larger than size criteria [organs ≥ 1 cm in

longest diameter, lymph nodes ≥ 2.5 cm in short axis, bones (soft tissue component) ≥ 1 cm in longest diameter] had gallium (68Ga) gozetotide uptake less than or equal to uptake in normal liver.

Supportive care administered at the physician's discretion included: bone-targeted agents including zoledronic acid, denosumab, or other bisphosphonates; androgen deprivation therapy (ADT); palliative radiotherapy. Patients randomised to the change in ARPI arm were allowed to cross over to receive Pluvicto upon radiographic disease progression confirmed by blinded independent central review (BICR) or continue to receive any other therapy at the physician's discretion.

The primary efficacy endpoint was radiographic progression-free survival (rPFS) as determined by BICR per Prostate Cancer Working Group 3 (PCWG3) criteria. The key secondary efficacy endpoint was overall survival (OS). Additional efficacy endpoints were time to first symptomatic skeletal event (SSE), PSA50 response, overall response rate (ORR), and an updated rPFS analysis at the time of third interim OS analysis.

Demographic and baseline disease characteristics were balanced between the treatment arms. The median age was 72 years (range: 43 to 94 years); 91% White; 2.6% Black or African American; 0.6% Asian; 99% had ECOG PS0-1. Randomisation was stratified by setting of prior ARPI use (castration-resistant prostate cancer (CRPC) vs. hormone-sensitive prostate cancer (HSPC)) and by symptomatology (asymptomatic or mildly symptomatic vs. symptomatic (score >3 on item 3 of the Brief Pain Inventory-Short Form (BPI-SF) questionnaire)).

Efficacy results for PSMAfore are presented in Table 3 and Figure 1. At the primary analysis (data cut-off (DCO) date: 02-Oct-2022), treatment with Pluvicto demonstrated a statistically significant improvement in rPFS by BICR compared to a change in ARPI therapy. There was an estimated 59% risk reduction of radiographic disease progression or death. An updated analysis of rPFS was conducted at the time of the third interim OS analysis (DCO date: 27-Feb-2024) and the results were consistent with the primary analysis. The final analysis of OS (DCO date: 01-Jan-2025) was conducted after the occurrence of 299 deaths without accounting for crossover, following the intent-to-treat (ITT) principle.

Table 3 Efficacy results in PSMAfore

Efficacy parameters	**Pluvicto**	**Change in ARPI**
Primary efficacy endpoints		
Radiographic progression-free survival (rPFS)[a]	N = 233	N = 234
Events (progression or death), n (%)	60 (25.8%)	106 (45.3%)
Radiographic progressions, n (%)	53 (22.7%)	99 (42.3%)
Deaths, n (%)	7 (3.0%)	7 (3.0%)
Hazard ratio (95% CI)[b]	0.41 (0.29, 0.56)	
P-value[c]	<0.001	
Median, months (95% CI)[d]	9.3 (6.8, NE)	5.6 (4.0, 6.0)
Updated median, months (95% CI)[e]	11.6 (9.3, 14.2)	5.6 (4.2, 6.0)
Key secondary efficacy endpoints		
Overall survival (OS)[f]	N = 234	N = 234
Deaths, n (%)	142 (60.7%)	157 (67.1%)

Median, months (95% CI)[d]	24.5 (19.5, 28.9)	23.1 (19.6, 25.5)
Hazard ratio (95% CI)[b]	0.91 (0.72, 1.14)	
P-value[c]	0.20	
Additional secondary efficacy endpoints[g]		
Time to symptomatic skeletal event (SSE)	N = 234	N = 234
Events (SSE or death), n (%)	31 (13.2%)	68 (29.1%)
SSEs, n (%)	27 (11.5%)	63 (26.9%)
Deaths, n (%)	4 (1.7%)	5 (2.1%)
Median, months (95% CI)[d]	NE	18.0 (14.3, NE)
Hazard ratio (95% CI)[b]	0.41 (0.26, 0.63)	
PSA50 response	N = 220	N = 226
PSA50 response rate, n (%)	113 (51.4%)	39 (17.3%)
Best overall response (BOR)		
Patients with measurable disease at baseline[h]	N = 72	N = 72
Complete response (CR), n (%)	15 (20.8%)	2 (2.8%)
Partial response (PR), n (%)	20 (27.8%)	8 (11.1%)
Stable disease (SD), n (%)	21 (29.2%)	30 (41.7%)
Progressive disease (PD), n (%)	14 (19.4%)	27 (37.5%)
Unknown, n (%)	2 (2.8%)	5 (6.9%)
Overall response rate (ORR)[h,i,j]	35 (48.6%)	10 (13.9%)

Abbreviations: CI, confidence interval; NE, not estimable; BICR, blinded independent central review; PCWG3, prostate cancer working group 3; RECIST, response evaluation criteria in solid tumors.

[a]By BICR per PCWG3 criteria. Based on data cut-off (DCO) date 02-Oct-2022.

[b]Hazard ratio based on the stratified Cox PH model. Hazard ratio <1 favors Pluvicto.

[c]Stratified log-rank test one-sided p-value.

[d]Based on Kaplan-Meier estimate.

[e]Median from third interim OS analysis based on 468 patients (234 Pluvicto arm, 234 control arm). Compared to the primary analysis, the median study duration from randomisation to DCO increased from 7.3 months to 24.1 months.

[f]DCO date: 01-Jan-2025.

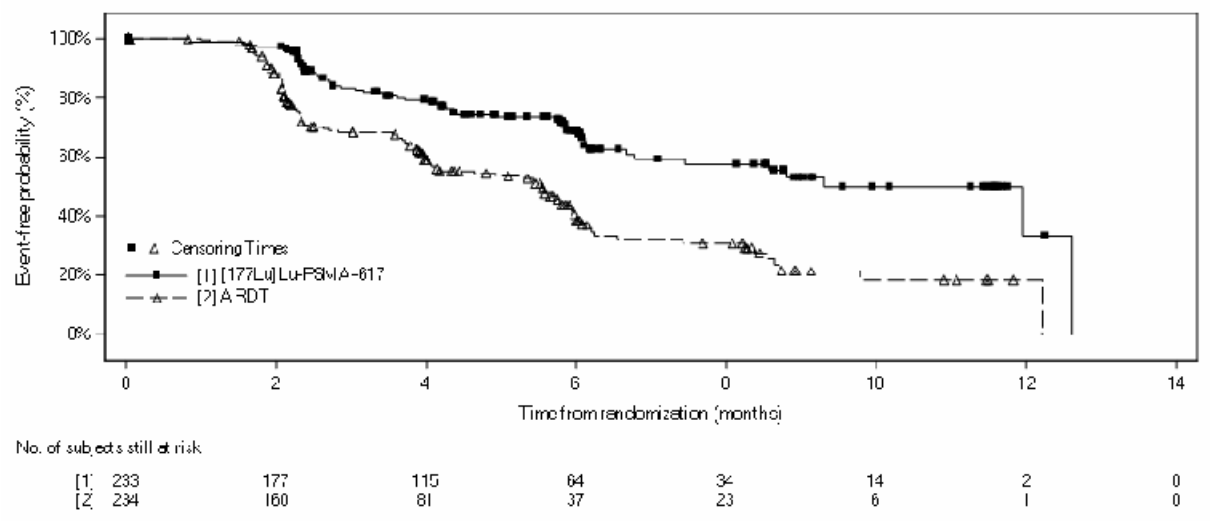
[g]DCO date for all additional secondary efficacy endpoints is 27-Feb-2024.

[h]Responses are based on soft tissue and bone lesion assessment. DCO date 27-Feb-2024.

[i]By BICR per RECIST v1.1.

[j]ORR: CR+PR. Confirmed response for CR and PR.

Figure 1 Kaplan-Meier plot of BICR-assessed radiographic progression-free survival (rPFS) in PSMAfore



Stratified log-rank test and stratified Cox model using strata per Interactive Response Technology (IRT) defined by setting of prior ARPI use and by symptomatology.
n/N: Number of events/number of patients in treatment arm.

Based on 27-Feb-2024 DCO, FACT-P total score showed an estimated 39% risk reduction of worsening from baseline, clinical progression or death based on hazard ratios in favor of Pluvicto, indicating patient stabilisation and delay in time to deterioration while on Pluvicto treatment. Specifically, time to worsening of the FACT-P total score was delayed by 3.2 months for Pluvicto with a median time to deterioration of 7.5 months (95% CI: 6.1, 8.5) compared to 4.3 months (95% CI: 3.5, 4.5) in the change in ARPI arm.

BPI-SF pain intensity scale showed an estimated 28% risk reduction of worsening from baseline, clinical progression or death based on hazard ratios in favor of Pluvicto, indicating patient stabilisation and less pain while on Pluvicto treatment. Specifically, time to worsening of the BPI-SF pain intensity scale was delayed by 1.3 months for Pluvicto with a median time to deterioration of 5.0 months (95% CI: 4.4, 6.8) compared to 3.7 months (95% CI: 3.1, 4.4) in the change in ARPI arm.

VISION Study:

The efficacy of Pluvicto in patients with progressive, PSMA-positive mCRPC was established in VISION, a randomised, multicentre, open-label phase III study. Eight hundred and thirty-one (N=831) adult patients were randomised (2:1) to receive either Pluvicto 7,400 MBq every 6 weeks for up to a total of 6 doses plus best standard of care (BSoC) (N=551) or BSoC alone (N=280).

Eligible patients were required to have PSMA-positive mCRPC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, at least one metastatic lesion present on computed tomography (CT), magnetic resonance imaging (MRI) or bone scan imaging, and adequate renal, hepatic and haematological function. Eligible patients were also required to have received at least one AR pathway inhibitor, such as abiraterone acetate or enzalutamide, and 1 or 2 prior taxane-based chemotherapy regimens (with a regimen defined as a minimum exposure of 2 cycles of a taxane). Patients with unstable symptomatic central nervous system metastases or symptomatic

or clinically/radiologically impending spinal cord compression were not eligible for the study. Patients underwent a gallium (^{68}Ga) gozetotide positron emission tomography (PET) scan to evaluate PSMA expression in lesions defined by central read criteria. Eligible patients were required to have at least one PSMA-positive lesion identified by this scan, and no CT/MRI measurable lesions that showed poor or no gallium (^{68}Ga) gozetotide uptake on the PET scan.

BSoC administered at the physician's discretion included: supportive measures including pain medications, hydration, blood transfusions, etc.; ketoconazole; radiation therapy (including seeded form or any external beam radiotherapy [including stereotactic body radiotherapy and palliative external beam]) to localised prostate cancer targets; bone-targeted agents including zoledronic acid, denosumab and any bisphosphonates; androgen-reducing agents including any corticosteroid and 5-alpha reductases; AR pathway inhibitors. BSoC excluded investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes, and hemi-body radiotherapy treatment.

Patients continued randomised treatment until evidence of tumour progression (based on investigator assessment per Prostate Cancer Working Group 3 [PCWG3] criteria), unacceptable toxicity, use of prohibited treatment, non-compliance or withdrawal, or lack of clinical benefit.

The alternate primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS) by blinded independent central review (BICR) per PCWG3 criteria. Additional secondary efficacy endpoints were overall response rate (ORR) by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and time to first symptomatic skeletal event (SSE) defined as first new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death from any cause, whichever occurred first.

Demographic and baseline disease characteristics were balanced between the treatment arms. The median age was 71 years (range: 40 to 94 years); 86.8% White; 6.6% Black or African American; 2.4% Asian; 92.4% had ECOG PS0-1; 7.6% had ECOG PS2. Randomisation was stratified by baseline lactase dehydrogenase (LDH), presence of liver metastases, ECOG PS score and inclusion of an AR pathway inhibitor as part of BSoC at the time of randomisation. At randomisation, all patients (100.0%) had received at least one prior taxane-based chemotherapy regimen and 41.2% of patients had received two. At randomisation, 51.3% of patients had received one prior AR pathway inhibitor, 41.0% of patients had received 2, and 7.7% of patients had received 3 or more. During the randomised treatment period, 52.6% of patients in the Pluvicto plus BSoC arm and 67.8% of patients in the BSoC alone arm received at least one AR pathway inhibitor.

Efficacy results for VISION are presented in Table 4 and Figures 2 and 3. The final analyses of OS and rPFS were event-driven and conducted after the occurrence of 530 deaths and 347 events, respectively. Treatment with Pluvicto plus BSoC demonstrated a statistically significant improvement in OS and rPFS by BICR compared to treatment with BSoC alone. The primary efficacy results are supported by a statistically significant difference between the treatment arms in the time to first

SSE ($p < 0.001$) and ORR ($p < 0.001$). There was an estimated 38% risk reduction of death, an estimated 60% risk reduction of radiographic disease progression or death, and an estimated 50% risk reduction of SSE or death based on hazard ratios in favour of Pluvicto plus BSoC treatment.

Table 4 Efficacy results in VISION

Efficacy parameters	Pluvicto plus BsoC	BSoC
Alternate primary efficacy endpoints		
Overall survival (OS)[a]	N = 551	N = 280
Deaths, n (%)	343 (62.3%)	187 (66.8%)
Median, months (95% CI)[b]	15.3 (14.2; 16.9)	11.3 (9.8; 13.5)
Hazard ratio (95% CI)[c]	0.62 (0.52; 0.74)	
P-value[d]	<0.001	
Radiographic progression-free survival (rPFS)[e,f]	N = 385	N = 196
Events (progression or death), n (%)	254 (66.0%)	93 (47.4%)
Radiographic progressions, n (%)	171 (44.4%)	59 (30.1%)
Deaths, n (%)	83 (21.6%)	34 (17.3%)
Median, months (95% CI)[b]	8.7 (8.3; 10.5)	3.4 (2.4; 4.0)
Hazard ratio (95% CI)[c]	0.40 (0.31; 0.52)	
P-value[d]	<0.001	
Secondary efficacy endpoints		
Time to first symptomatic skeletal event (SSE)[f]	N = 385	N = 196
Events (SSE or death), n (%)	256 (66.5%)	137 (69.9%)
SSEs, n (%)	60 (15.6%)	34 (17.3%)
Deaths, n (%)	196 (50.9%)	103 (52.6%)
Median, months (95% CI)[b]	11.5 (10.3; 13.2)	6.8 (5.2; 8.5)
Hazard ratio (95% CI)[c]	0.50 (0.40; 0.62)	
P-value[g]	<0.001	
Best overall response (BOR)		
Patients with evaluable disease at baseline	N = 319	N = 120
Complete response (CR), n (%)	18 (5.6%)	0 (0%)
Partial response (PR), n (%)	77 (24.1%)	2 (1.7%)
Stable disease (SD), n (%)	68 (21.3%)	30 (25.0%)
Non-CR/Non-PD, n (%)	121 (37.9%)	48 (40.0%)
Progressive disease (PD), n (%)	33 (10.3%)	35 (29.2%)
Unknown, n (%)	2 (0.6%)	5 (4.2%)
Overall response rate (ORR)[h,i]	95 (29.8%)	2 (1.7%)
P-value[j]	<0.001	
Duration of response (DOR)[h]		
Number of responders	N = 95	N = 2
Events (progression or death), n (%)	46 (48.4%)	1 (50.0%)
Radiographic progressions, n (%)	29 (30.5%)	1 (50.0%)
Deaths, n (%)	17 (17.9%)	0 (0%)
Median, months (95% CI)[b]	9.8 (9.1; 11.7)	10.6 (NE; NE)[k]

BSoC: Best standard of care; CI: Confidence interval; NE: Not evaluable; BICR: Blinded independent central review; PCWG3: Prostate Cancer Working Group 3; RECIST: Response Evaluation Criteria in Solid Tumors.

[a] Analysed on an ITT basis in all randomised patients.

[b] Based on Kaplan-Meier estimate.

[c] Hazard ratio based on the stratified Cox PH model. Hazard ratio <1 favours Pluvicto plus BSoC.

[d] Stratified log-rank test one-sided p-value.

[e] By BICR per PCWG3 criteria. The primary analysis of rPFS included censoring of patients who had ≥2 consecutive missed tumour assessments immediately prior to progression or death. Results for rPFS with and without censoring for missed assessments were consistent.

[f] Analysed on an ITT basis in all patients randomised on or after 05-Mar-2019, when actions were implemented to mitigate early drop out from BSoC arm.

[g] Stratified log-rank test two-sided p-value.

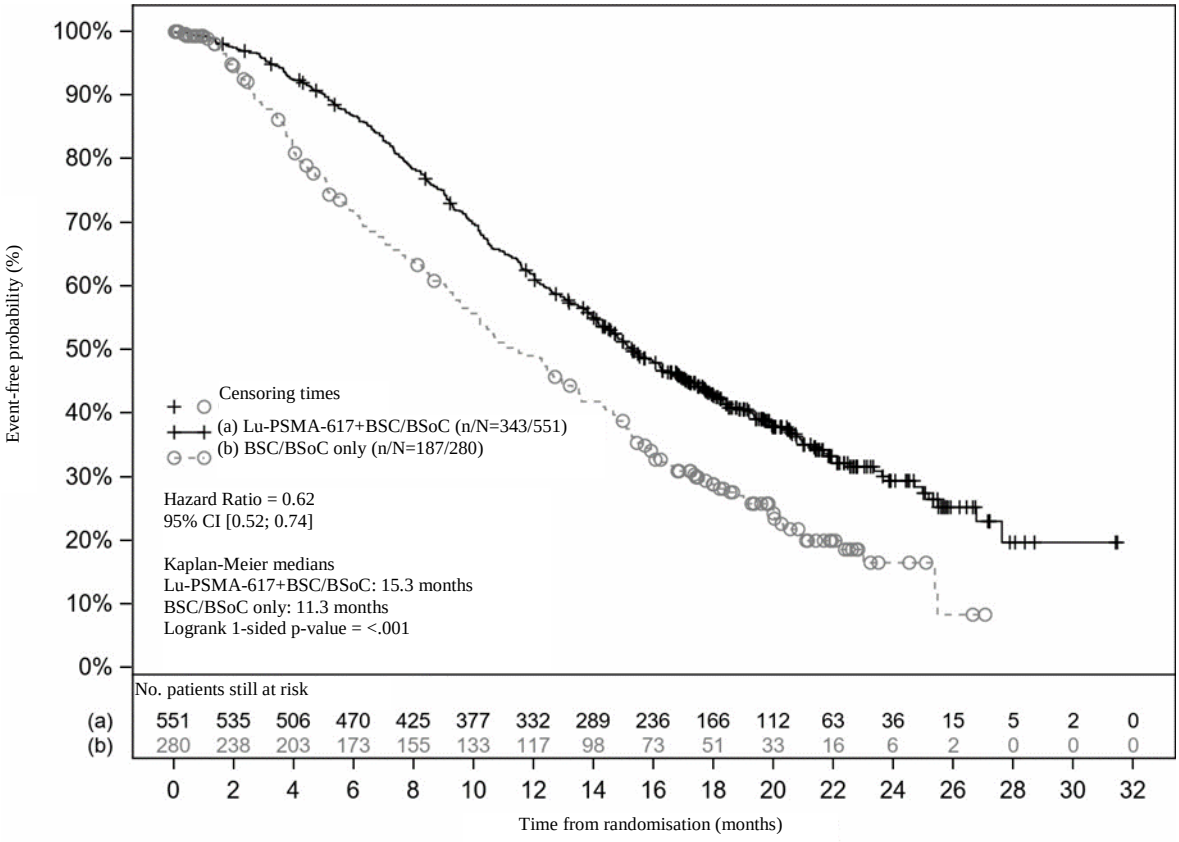
[h] By BICR per RECIST v1.1.

[i] ORR: CR+PR. Confirmed response for CR and PR.

[j] Stratified Wald's Chi-square test two-sided p-value.

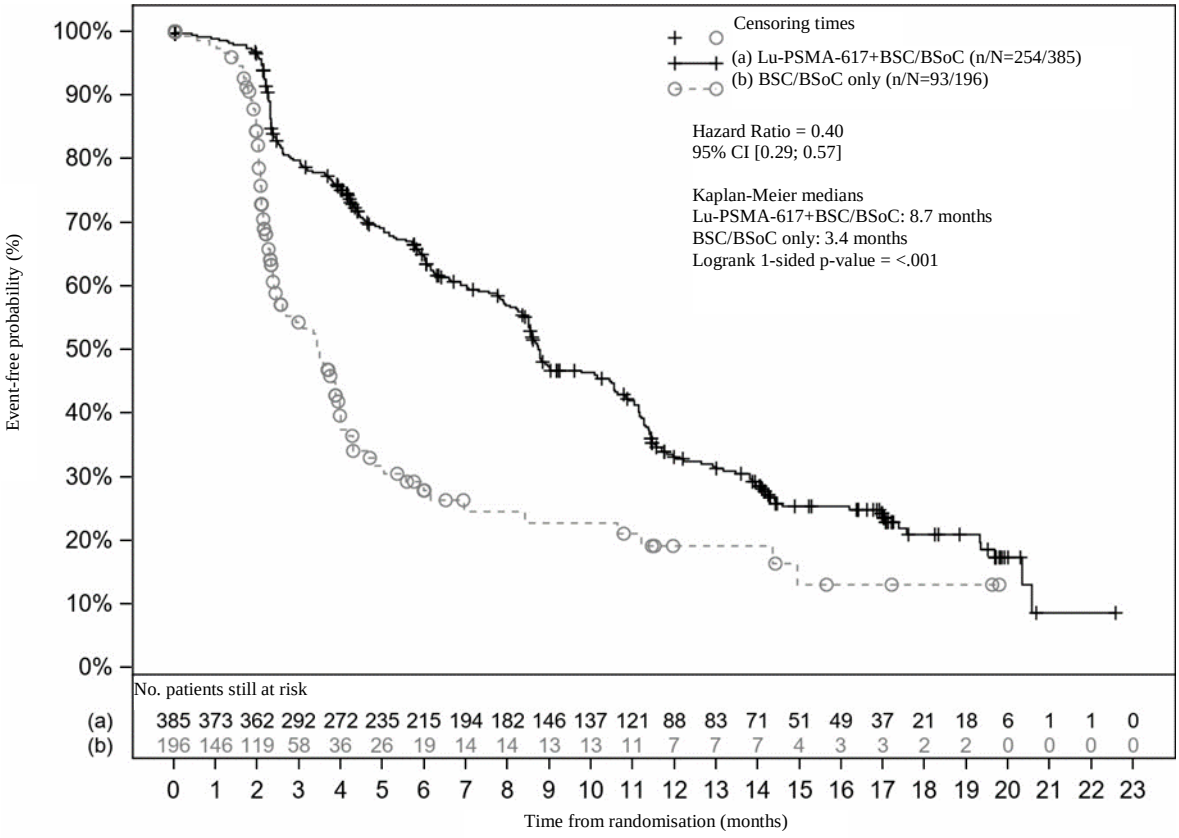
[k] Median DOR in the BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST v1.1 radiographic progression or death.

Figure 2 Kaplan-Meier plot of overall survival in VISION



Stratified log-rank test and stratified Cox model using strata per Interactive Response Technology (IRT) defined by LDH level, presence of liver metastases, ECOG score and inclusion of an AR pathway inhibitor in BSoC at time of randomisation.
n/N: Number of events/number of patients in treatment arm.

Figure 3 Kaplan-Meier plot of BICR-assessed radiographic progression-free survival (rPFS) in VISION



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of an AR pathway inhibitor in BSoC at time of randomisation.
n/N: Number of events/number of patients in treatment arm.

Mean and median baseline prostate-specific antigen (PSA) levels were similar in both treatment arms. Serum PSA levels decreased by ≥50% from baseline in 177 of 385 (46.0%) patients who received Pluvicto plus BSoC and in 14 of 196 (7.1%) patients who received BSoC alone.

FACT-P total score showed an estimated 46% risk reduction of worsening from baseline, clinical progression or death based on hazard ratios in favour of Pluvicto plus BSoC, indicating patient stabilisation and delay in time to deterioration while on Pluvicto plus BSoC treatment. Specifically, time to worsening of the FACT-P total score was delayed by 3.5 months for Pluvicto plus BSoC with a median time to deterioration of 5.7 months (95% CI: 4.8, 6.6) compared to 2.2 months (95% CI: 1.8, 2.8) for BSoC alone. BPI-SF pain intensity scale showed an estimated 48% risk reduction of worsening from baseline, clinical progression or death based on hazard ratios in favour of Pluvicto plus BSoC, indicating patient stabilisation and less pain while on Pluvicto plus BSoC treatment. Specifically, time to worsening of the BPI-SF pain intensity scale was delayed by 3.7 months for Pluvicto plus BSoC with a median time to deterioration of 5.9 months (95% CI: 4.8, 6.9) compared to 2.2 months (95% CI: 1.8, 2.8) for BSoC alone.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Pluvicto in all subsets of the paediatric population in the treatment of PSMA-expressing prostate cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of lutetium (^{177}Lu) vipivotide tetraxetan have been characterised in 30 patients in the phase III VISION sub-study.

Absorption

Pluvicto is administered intravenously and is immediately and completely bioavailable.

The geometric mean blood exposure (area under the curve [AUC_{inf}]) for lutetium (^{177}Lu) vipivotide tetraxetan at the recommended dose is 52.3 ng.h/mL (geometric mean coefficient of variation [CV] 31.4%). The geometric mean maximum blood concentration (C_{max}) for lutetium (^{177}Lu) vipivotide tetraxetan at the recommended dose is 6.58 ng/mL (CV 43.5%).

Distribution

The geometric mean volume of distribution (V_z) for lutetium (^{177}Lu) vipivotide tetraxetan is 123 L (CV 78.1%).

Vipivotide tetraxetan and non-radioactive lutetium (^{175}Lu) vipivotide tetraxetan are each 60% to 70% bound to human plasma proteins.

Organ uptake

The biodistribution of lutetium (^{177}Lu) vipivotide tetraxetan shows primary uptake in lacrimal glands, salivary glands, kidneys, urinary bladder wall, liver, small intestine and large intestine (left and right colon).

Elimination

The geometric mean clearance (CL) for lutetium (^{177}Lu) vipivotide tetraxetan is 2.04 L/h (CV 31.5%).

Lutetium (^{177}Lu) vipivotide tetraxetan is primarily eliminated renally.

Half-life

Pluvicto shows a bi-exponential elimination with a geometric mean terminal elimination half-life ($T_{½}$) of 41.6 hours (CV 68.8%).

Biotransformation

Lutetium (^{177}Lu) vipivotide tetraxetan does not undergo hepatic or renal metabolism.

In vitro drug interaction potential

CYP450 enzymes
Vipivotide tetraxetan is not a substrate of cytochrome P450 (CYP450) enzymes. It does not induce cytochrome P450 (CYP) 1A2, 2B6 or 3A4, and it does not inhibit cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 *in vitro*.

Transporters
Vipivotide tetraxetan is not a substrate of BCRP, Pgp, MATE1, MATE2K, OAT1, OAT3 or OCT2, and it is not an inhibitor of BCRP, Pgp, BSEP, MATE1, MATE2K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2 *in vitro*.

Elderly

Of the 227 patients randomised to the Pluvicto arm who received at least one dose of Pluvicto in the PSMAfore study, 177 patients (78%) were 65 years or older and 83 patients (37%) were 75 years or older.

Of the 529 patients who received at least one dose of Pluvicto plus BSoC in the VISION study, 387 patients (73%) were aged 65 years or older and 143 patients (27%) were aged 75 years or older.

Effects of age, body weight and renal impairment

No clinically significant effects on the pharmacokinetic parameters of lutetium (^{177}Lu) vipivotide tetraxetan were identified for the following covariates assessed in 30 patients in the phase III VISION sub-study: age (median: 67 years; range: 52 to 80 years) and body weight (median: 88.8 kg; range: 63.8 to 143.0 kg). Exposure (AUC) of lutetium (^{177}Lu) vipivotide tetraxetan increased with decreasing creatinine clearance (CLcr), however CLcr $\geq$54 mL/min (Cockcroft Gault) did not have a clinically meaningful effect on the pharmacokinetics of lutetium (^{177}Lu) vipivotide tetraxetan.

Cardiac electrophysiology

The ability of Pluvicto to prolong the QTc interval at the recommended dose was assessed in 30 patients in the phase III VISION sub-study. Pluvicto did not prolong the QT/QTc interval.

5.3 Preclinical safety data

No toxicological effects were observed in safety pharmacology or single-dose toxicity studies in rats and minipigs administered a non-radioactive formulation containing vipivotide tetraxetan and lutetium (^{175}Lu) vipivotide tetraxetan, or in repeat-dose toxicity studies in rats administered vipivotide tetraxetan.

Mutagenicity and long-term carcinogenicity studies have not been carried out with lutetium (^{177}Lu) vipivotide tetraxetan; however, radiation is a carcinogen and mutagen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid

Sodium acetate

Gentisic acid

Sodium ascorbate

Pentetic acid

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

120 hours (5 days) from the date and time of calibration.

6.4 Special precautions for storage

Do not freeze.

Store in the original package in order to protect from ionising radiation (lead shielding).

Storage of radiopharmaceuticals should be in accordance with national regulations on radioactive materials.

6.5 Nature and contents of container

Clear, colourless type I glass vial, closed with a bromobutyl rubber stopper and aluminum seal.

Each vial contains a volume of solution that can range from 7.5 mL to 12.5 mL corresponding to a radioactivity of 7,400 MBq at the date and time of administration.

The vial is enclosed within a lead container for protective shielding.

6.6 Special precautions for disposal

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.

For instructions on preparation of the medicinal product before administration, see section 12.

If at any time in the preparation of this medicinal product the integrity of this vial is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

The surface dose rates and the accumulated dose depend on many factors. Measurements on the location and during work are critical and should be practiced for more precise and instructive determination of overall radiation dose to the staff. Healthcare personnel are advised to limit the time of close contact with patients administered lutetium (^{177}Lu) vipivotide tetraxetan. The use of television monitor systems to monitor the patients is recommended. Given the half-life of lutetium-177, it is specially recommended to avoid internal contamination. It is necessary to use protective high quality (latex/nitrile) gloves to avoid direct contact with the radiopharmaceutical (vial/syringe). For minimising radiation exposure, always use the principles of time, distance and shielding (reducing the manipulation of the vial and using the material already supplied par the manufacturer).

This preparation is likely to result in a relatively high radiation dose to most patients. The administration of Pluvicto may result in significant environmental hazard. This may be of concern to the immediate family of those individuals undergoing treatment or the general public depending on the level of radioactivity administered hence radioprotection rules should be followed (section 4.4). Suitable precautions in

accordance with national regulations should be taken concerning the radioactivity eliminated by the patients in order to avoid any contaminations.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Lutetium-177 for Pluvicto is prepared using the stable nuclide ytterbium-176 (“non-carrier added”).

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited,
2nd Floor, The WestWorks Building, White City Place,
195 Wood Lane, London, W12 7FQ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00101/1233

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

16/01/2026

11 DOSIMETRY

Dosimetry of lutetium (^{177}Lu) vipivotide tetraxetan was collected in 29 patients in the phase III VISION sub-study, in order to calculate whole body and organ radiation dosimetry. The mean and standard deviation (SD) of the estimated radiation absorbed doses to different organs for adult patients receiving Pluvicto are shown in Table 4. The organs with the highest radiation absorbed doses are lacrimal glands and salivary glands.

The maximum penetration of lutetium-177 in tissue is approximately 2 mm and the mean penetration is 0.67 mm.

Table 4 Estimated radiation absorbed dose[a] for Pluvicto in the VISION sub-study

	Absorbed dose per unit activity (mGy/MBq) (N=29)		Calculated absorbed dose for 7,400 MBq administration (mGy)		Calculated absorbed dose for 6 x 7,400 MBq (44,400 MBq cumulative activity) (mGy)	
Organ	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Adrenals	0.033	0.025	0.24	0.19	1.5	1.1
Brain	0.007	0.005	0.049	0.035	0.30	0.22
Eyes	0.022	0.024	0.16	0.18	0.99	1.1
Gallbladder wall	0.028	0.026	0.20	0.19	1.2	1.1
Heart wall	0.17	0.12	1.2	0.83	7.8	5.2
Kidneys	0.43	0.16	3.1	1.2	19	7.3
Lacrimal glands	2.1	0.47	15	3.4	92	21
Left colon	0.58	0.14	4.1	1.0	26	6.0
Liver	0.090	0.044	0.64	0.32	4.0	2.0
Lungs	0.11	0.11	0.76	0.81	4.7	4.9
Oesophagus	0.025	0.026	0.18	0.19	1.1	1.1
Osteogenic cells	0.036	0.028	0.26	0.21	1.6	1.3
Pancreas	0.027	0.026	0.19	0.19	1.2	1.1
Prostate	0.027	0.026	0.19	0.19	1.2	1.1
Red marrow	0.035	0.020	0.25	0.15	1.5	0.90
Rectum	0.56	0.14	4.0	1.1	25	6.2
Right colon	0.32	0.078	2.3	0.58	14	3.4
Salivary glands	0.63	0.36	4.5	2.6	28	16
Small intestine	0.071	0.031	0.50	0.23	3.1	1.4
Spleen	0.067	0.027	0.48	0.20	3.0	1.2
Stomach wall	0.025	0.026	0.18	0.19	1.1	1.1
Testes	0.023	0.025	0.16	0.18	1.0	1.1
Thymus	0.025	0.026	0.18	0.19	1.1	1.1
Thyroid	0.26	0.37	1.8	2.7	11	16
Total body	0.037	0.027	0.27	0.20	1.6	1.2
Urinary bladder wall	0.32	0.025	2.3	0.19	14	1.1

[a] Values have been calculated based on dosimetry estimates at full precision and rounded to relevant digits.

Radiation dose to specific organs, which may not be the target organ of therapy, can be influenced significantly by pathophysiological changes induced by the disease process. This should be taken into consideration when using the following information.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single-dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.

Quality control

The solution should be visually inspected for damage and contamination before use, and only clear solutions free of visible particles should be used. The visual inspection of the solution should be performed under a shielded screen for radioprotection purposes. The vial must not be opened.

If at any time in the preparation of this medicinal product the integrity of the vial is compromised, it should not be used.

The amount of radioactivity in the vial must be measured prior to administration using a suitable radioactivity calibration system in order to confirm that the actual amount of radioactivity to be administered is equal to the planned amount at the administration time.