EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 October 2022
EMA/CHMP/954737/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Locametz

International non-proprietary name: gozetotide

Procedure No. EMEA/H/C/005488/0000

Note

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

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List of abbreviations

AAA	Advanced Accelerator Applications
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ASMF	Active Substance Master File
BCR	Biochemical recurrence
BCRP	Breast cancer resistance protein
BSC/BSoC	Best supportive care/best standard of care
BSEP	Bile Salt Export Pump
C1D1	Cycle 1 Day 1
CHMP	Committee for Medicinal Products for Human use
COVID-19	Coronavirus disease-19
cGMP	current Good Manufacturing Practice
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
CYP	Cytochrome
DCR	Disease control rate
DKFZ	Deutsches Krebsforschungszentrum (German Cancer Research Center)
DoR	Duration of response
EANM	European Association of Nuclear Medicine
EC	European Commission
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FT-IR	Fourrier Transform Infrared Spectroscopy
GCP	Good Clinical Practice

GC Gas Chromatography

GC-MS Gas chromatography mass spectrometry

GMP Good Manufacturing Practice

HA Health Authority

HBED-CC N,N'-Bis-[2-hydroxy-5-(carboxyethyl)-benzyl]-ethylenediamine-N,N'-diacetic acid

HDPE High Density Polyethylene

HPLC High performance liquid chromatography

HPLC-UV-DAD High-performance liquid chromatography–ultraviolet- diode array detection

IC Ion chromatography

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IND Investigational New Drug

IPC In-process control

IR Infrared

MAA Marketing authorization application

MATE Multidrug And Toxic Compound Extrusion

MBq Megabequerel

mCi Millicurie

mCRPC Metastatic castration-resistant prostate cancer

MedDRA Medical Dictionary for Regulatory Activities

mGy Milligray

MO Major Objection

MRI Magnetic resonance imaging

MS Mass Spectrometry

mSv Millisievert

NAAD Novel androgen axis drugs

NDA New Drug Application

NMR Nuclear Magnetic Resonance

NOAEL No-observed-adverse-effect-level

NPV Negative predictive value

OAT Organic anion transporters

OCT Organic cation transporter

ORR Overall response rate

OS	Overall survival
PD	Pharmacodynamics
PET	Positron emission tomography
PETG	Polyethylene Terephthalate glycol
Ph. Eur.	European Pharmacopoeia
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPV	Positive predictive value
PSA	Prostate-specific antigen
PSMA	Prostate specific membrane antigen
PT	Preferred term
RLT	Radioligand therapy
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SBP	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SD	Standard deviation
SmPC	Summary of Product Characteristics
SNMMI	Society for Nuclear Medicine and Medical Imaging
SOC	System organ class
SSE	Symptomatic skeletal event
SUVmax	Maximum standardized uptake value
TEAE	Treatment-emergent adverse event
TFA	Trifluoroacetic acid
TNM	Tumour, nodes, metastases
UCLA	University of California, Los Angeles
UCSF	University of California, San Francisco (Medical Center)
US	United States
USPI	United States Prescribing Information
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 30 September 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Locametz, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 October 2019.

The applicant applied for the following indication:

Locametz, after radiolabelling with gallium-68, is a radioactive diagnostic agent indicated for the identification of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET) in adult patients with prostate cancer.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0290/2019 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

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

1.6. Scientific advice

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

Date	Reference	SAWP co-ordinators
26 April 2019	EMEA/H/SA/4079/1/2019/III	Martin Mengel, Serena Marchetti

The Scientific advice pertained to the following non-clinical and clinical aspects:

- Sufficiency of the proposed nonclinical data package to support a Marketing Authorisation Application (MAA).
- Acceptability of the overall clinical development plan to support a MAA.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig Co-Rapporteur: Paula Boudewina van Hennik

The application was received by the EMA on	30 September 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	1 July 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 July 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	21 July 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 August 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	2 September 2022

The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 September 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 September 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 September 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Locametz on	13 October 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	13 October 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially applied indication for Locametz was, after radiolabelling with gallium-68, as a radioactive diagnostic agent for the identification of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET) in adult patients with prostate cancer.

The finally approved indication for Locametz, after radiolabelling with gallium-68, is 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 primary curative therapy,

• Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy,

• Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated.

2.1.2. Epidemiology

Prostate cancer (PCa) is the second leading cause of cancer-related death among men in the US (Siegel et al 2020) and the third leading cause of cancer-related death in Europe (Malvezzi et al 2019). In addition to the mortality burden, prostate cancer results in a significant negative impact on quality of life (Diels et al 2015, Lloyd et al 2015). In the USA, approximately 191,930 new cases of PC and 33,330 deaths were estimated for 2020 (American Cancer Society 2020), and in Europe, the corresponding estimates were 473,344 new cases and 108,088 deaths (International Agency for Research on Cancer 2020).

2.1.3. Biologic features

Prostate-specific membrane antigen is a type II transmembrane protein, also known as folate hydrolase I or glutamate carboxypeptidase II, and is a biological target for diagnostic imaging and therapy in PCa (Silver et al 1997, O'Keefe et al 2018). PSMA is highly expressed in nearly all prostate cancers, including adenocarcinoma, but has restricted and several hundred-fold lower expression in some normal tissues such as the duodenal mucosa, renal proximal tubules, and salivary glands (Bostwick et al 1998, Sokoloff et al 2000, Chang 2004, Ghosh and Heston 2004). The differential expression of PSMA from tumour to non-tumour tissue allows for targeted localization of PCa and its metastases by means of ^{68}Ga-PSMA-11. Expression of PSMA is also an independent predictor of poor prognosis (Chang 2004, Hupe et al 2018) with significantly shorter survival and a higher risk of disease recurrence reported in patients with high levels of PSMA expression (Ross et al 2003, Cimadamore et al 2018, Hupe et al 2018, Nagaya et al 2020).

The binding of a high affinity ligand to PSMA leads to internalization through endocytosis, and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003, Benešová et al 2015). This functional feature of PSMA in addition to its expression pattern allows for the development of low-molecular weight targeted radiopharmaceuticals with favourable pharmacokinetic and tumour penetration properties (Haberkorn et al 2016).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The clinical picture of PCa is variable and may range between asymptomatic, microscopic, well-differentiated tumour that may never become clinically significant to the rarer screen detected, or clinically symptomatic aggressive, high-grade cancer that causes metastases, morbidity, and death. Diagnostic work-up of PCa is complex. Diagnostic tools include PSA testing, digital rectal palpation, transrectal ultrasound (TRUS), prostate biopsy, and histopathologic examination (Schwarzenböck et al 2012, Smith et al 2016, Prasad et al 2016). Additionally, further imaging techniques such as, magnetic resonance imaging (MRI), bone scintigraphy, computer tomography (CT), and positron emission tomography (PET)/CT with [18F]Fluorodeoxyglucose, [18F]Choline, [11C]Choline and the more recently approved [18F]fluciclovine are used (Schwarzenböck et al 2012; Nanni et al 2016, Odewole et al 2016).

Two main pivotal time-points in terms of decision-making on treatment strategy are primary staging of PCa, that takes place in the patients with confirmed PCa, before the first definitive therapy is started, and confirmation of PCa recurrence and staging in the patients who developed increased PSA after

curative treatment of PCa (i.e., patients with so called biochemical recurrence – BCR). In both cases, gained information can direct clinical decision-making and may have impact on subsequent treatment strategy and clinical outcomes, such as patients' survival.

The joint guideline on diagnosis and management of prostate cancer from European Association of Urology (EAU), European Association of Nuclear Medicine (EANM), European Society for Therapeutic Radiology and Oncology (ESTRO), European Society of Urogenital Radiology (ESUR) and International Society of Geriatric Oncology (SIOG) (Mottet et al., 2020) and the latest guideline from ESMO (Parker et al., 2020) recommend that for primary staging the patients with intermediate-risk disease are staged for metastases using MRI or CT (abdomen and pelvis) and bone scan and those with high-risk disease using CT (chest, abdomen and pelvis) and bone scan. Mottet et al., state that in the primary staging "PSMA PET/CT is more accurate for staging than CT and bone scan for high-risk disease but to date no outcome data exist to inform subsequent management" (level of evidence: 1b) and that "When using PSMA PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data

of subsequent treatment changes." (strength rating: strong). In this setting ESMO recommends not to base clinical decision-making on the outcomes of 68Ga-PSMA PET, as impact of this diagnostic tool on clinical outcomes has not been evaluated (Parker et al., 2020).

In the BCR population 68Ga-PSMA PET is recommended in the patients after radical prostatectomy only if the results may influence subsequent therapy (strength rating: "weak") and in the patients after radiotherapy if they are fit for curative salvage treatment (strength rating: "strong"). Also, choline PET/CT, fluciclovine PET/CT, multiparametric MRI (mpMRI) are being recommended depending on the specific patient population (Mottet et al.).

Overall, the experts acknowledge, that CT and MRI display poor sensitivity in diagnostics of PCa/Staging and that choline, fluciclovine and PSMA PET display better sensitivity.

In relation to use of 68Ga-PSMA PET for selection of patients for PSMA-targeted therapy, evidence is limited to the studies investigating ^{177}Lu-PSMA-617 treatment in the "PSMA-positive" population with metastasised castration resistant prostate cancer (mCRPC), selected for treatment by means of 68Ga-PSMA PET (Note: the studies include the VISION study conducted by the Applicant). This is reflected in the Joint Guideline on PCa (Mottet et al., 2022), that recommends that ^{177}Lu-PSMA-617 is offered to "pre-treated patients with mCRPC with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan". (strength rating: strong).

2.1.5. Management

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

The current standard of care in metastatic prostate cancer (mPC) is based on chemotherapy, androgen deprivation by different mechanisms of action on the hypothalamic-pituitary-gonadal axis, and adrenal-androgen receptor signaling. Standard ADT and NAADs (i.e. abiraterone acetate or enzalutamide) can stabilize metastatic castration-sensitive PCs (mCSPC) for many years. However, most patients eventually progress to mCRPC, which remains challenging to treat. One of the options available for the patients with mCRPC is ^{177}Lu-PSMA-617 therapy. This PSMA-targeted radio-ligand therapy utilizes a radiolabeled small-molecule ligand that binds with high affinity to PSMA, resulting in internalization and retention within the targeted prostate cancer cell (Ghosh and Heston 2004, Benešová et al 2015), delivering therapeutic radiation dose to cancer cells via PSMA while minimizing radiation-related side effects in the patients with PSMA-positive mCRPC. Identification of patients with PSMA-positive mCRPC prior to start of such therapy is a clinically relevant objective for ^{68}Ga-labelled PSMA-based PET. Notably, ^{177}Lu-PSMA-617 treatment has been approved in the US since 2021 and is

currently under evaluation for MA in Europe (centralised procedure EMEA/H/C/005483).

2.2. About the product

Gozetotide (PSMA-11) is constructed using a urea-based targeting ligand and the gallium chelating moiety HBED CC (Eder et al 2012, Eder et al 2014). The radioisotope gallium-68 (^{68}Ga) utilized with PSMA-11 is a β+ emitting radionuclide with a 68-minute physical half-life, and a high emission yield, that makes it a suitable PET imaging agent (Fendler et al 2017b). ^{68}Ga-labelled gozetotide ([^{68}Ga]Ga-PSMA-11) after intravenous administration specifically binds to prostate specific membrane antigen (PSMA), allowing identification of PSMA-expressing tissues with PET, including PCa. The differential expression of PSMA from tumour to non-tumour tissue allows for targeted localization of PCa and its metastases by means of ^{68}Ga-PSMA-11.

[^{68}Ga]Ga-PSMA-11 was developed at the German Cancer Research Center (Deutsches Krebsforschungszentrum) and University Hospital Heidelberg for the purpose of diagnostic imaging in patients with prostate cancer and has been under formal clinical development by Endocyte, and, subsequently, Advanced Accelerator Applications (AAA)/Novartis, since 2017.

The proposed commercial formulation of PSMA-11 (gozetotide; Tradename: Locametz) is a one-vial multi-dose kit for radiopharmaceutical preparation which must be reconstituted and radiolabeled with a sterile solution of ^{68}Ga in HCl coming from a cGMP-grade ^{68}Ge/^{68}Ga generator to obtain [^{68}Ga]Ga-PSMA-11 radiolabeled solution for injection. The obtained ^{68}Ga-PSMA-11 radiolabeled solution is complying with the frame given by the Ph. Eur. Monograph (3044) for "Gallium (^{68}Ga) PSMA-11 Injection". The PSMA-11 kit is intended for use in a radiopharmacy after radiolabeling with gallium-68.

This medicinal product should only be administered by trained healthcare professionals with technical expertise in using and handling nuclear medicine imaging agents and only in a designated nuclear medicine facility.
Posology: The recommended dose of gallium (^{68}Ga) gozetotide is 1.8-2.2 MBq/kg of body weight, with a minimum dose of 111 MBq up to a maximum dose of 259 MBq.

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, other diagnostic radiopharmaceuticals for tumour detection, ATC code: V09IX14.

In this document, the radiolabeled compound gallium (^{68}Ga) gozetotide or [^{68}Ga]Ga-PSMA-11 (company research code: AAA517) may be referred to as ^{68}Ga-PSMA-11, and the therapeutic agent lutetium (^{177}Lu) vipivotide tetraxetan (AAA617 / [^{177}Lu]Lu-PSMA-617) is referred to as ^{177}Lu-PSMA-617.

2.3. Type of Application and aspects on development

A scientific advice from the EU Scientific Advice Working Party was received on 10-Apr-2019 on non-clinical and clinical development package.

At the time of the scientific advice development of the product as a specific diagnostic tool for selection of patients for treatment with ^{177}Lu-PSMA-617 (MAA submitted as EMEA/H/C/5483) was intended, that was under development for the indication 'metastatic castration-resistant prostate cancer post NAAD and post taxane-containing chemotherapy'. Both investigational products ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 were to be tested in the same clinical study, that has now been submitted under the name of VISION (PSMA-617-01) study. The CHMP stated that within the context of the narrow indication (use of ^{68}Ga-PSMA-11 for patient selection of ^{177}LU-PSMA-617 treatment) "in conjunction with a positive benefit/risk of the therapeutic product ^{177}Lu-PSMA-617 in the population selected by use of

^{68}Ga-PSMA-11 as determined in the VISION trial, convincing technical performance (see "Reader agreement" below)" needed to be demonstrated." No dedicated large clinical studies were requested considering the envisaged restricted use of gozetotide.

The currently claimed indication covers prostate cancer (PCa) diagnostics in various clinical situations: primary staging, diagnosis of cancer after biochemical recurrence (BCR) and selection of the PSMA-positive patients for PSMA-targeted therapy. Thus, the requirements outlined in the CHMP advice only partly apply and the recommendations of relevant guidelines on diagnostic products (CHMP/EWP/1119/98 REV1 and CHMP/EWP/321180/2008) are to be followed.

The Applicant has conducted one international, prospective, open-label, multicenter, randomized Phase III study (study PSMA-617-01 - VISION) to evaluate efficacy of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC), in which ^{68}Ga-PSMA-11 was used for patient selection. Additionally, a reviewer variability study was conducted using the ^{68}Ga-PSMA-11 PET images from VISION study and dosimetry calculations based on the raw data collected by Sandgren et al. (2019) have been performed. The remaining evidence to substantiate this submission is provided from published literature.

Some requirements for the relevant guidance have not been addressed. Specifically, impact on clinical outcomes remains unknown. However, this limitation has been mentioned in the product information.

Notably, the final to-be-marketed product under the MAA has not been tested in humans and no dedicated bridging study has been conducted, based on the rationale that no bioequivalence studies are required for water-soluble i.v. formulations containing the same active substance in accordance with the EMA guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

The proposed pH specification is lower than foreseen by the Pharmacopeia monograph "Gallium (^{68}Ga) PSMA-11 Injection" (Eur. Ph. 3044) and more, or different type of injection site reactions (e.g., injection site pain) than currently documented are expected. The Applicant refers to another diagnostic product with similarly low pH (pH 3.2 – 3.8) SomaKit TOC (by Advanced Accelerator Applications; EMEA/H/C/004140; approved in 2016), that has been approved and is in use with a single adverse drug reaction (ADR) - "injection site pain" - reported thus far. Osmolality of ^{68}Ga-Locametz may not be similar to the products applied in the published studies. However, this is estimated to be roughly within the range of 600-800 mOsm/kg, which is below the threshold of tolerability of 1000 mOsm/kg acknowledged for i.v. small volume (≤100 mL) injections (Wang et al., https://doi.org/10.1016/j.ijpharm.2015.05.069). Thus, the bridging to the products used in the published studies is considered established, with some remaining uncertainty regarding the frequency of injection site reactions.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as kit for radiopharmaceutical preparation containing 25 micrograms of gozetotide (PSMA-11).

The kit has to be radiolabelled and prepared to an injection in combination with a solution of [^{68}Ga]Gallium in diluted hydrochloric acid provided by a ^{68}Ge/^{68}Ga radionuclide generator to obtain [^{68}Ga]Ga-PSMA-11 solution for injection (so called [^{68}Ga]gallium-PSMA-11 solution for injection), being

the radiolabelled imaging product, which can be directly injected to the patient. The radionuclide is not part of the kit.

Other ingredients of the kit are: gentisic acid, sodium acetate trihydrate, and sodium chloride.

The product is available in 10 mL type I Plus glass vial closed with a rubber stopper and sealed with a flip-off cap as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

Gozetotide (PSMA-11) is a synthetic ligand that contains 2 ureido-linked amino acids (Glu and Lys), the linker Ahx is bound to the side chain amino acid group of the Lys residue and the chelator HBED-CC. Gozetotide (PSMA-11) is isolated as non – stoichiometric Gozetotide (PSMA-11) – trifluoro acetate compound.

Gozetotide (PSMA-11) is a cold chemical precursor dedicated to be radiolabelled with the radionuclide "gallium-68" to form the clinical relevant active substance [^{68}Ga]Gallium-gozetotide used for diagnostic radiopharmaceutical for Positron Emission Tomography (PET).

In a kit for radiopharmaceutical preparation the cold non-radiolabelled active substance is per definition the active substance to be declared for the kit.

The chemical name of gozetotide is (2S)-2-[[(1S)-1-carboxy-5-[6-[3-[3-[[2-[[5-(2-carboxyethyl)-2-hydroxyphenyl]methyl-(carboxymethyl)amino]ethyl-(carboxymethyl)amino]methyl]-4-hydroxyphenyl]propanoylamino]hexanoylamino]pentyl]carbamoylamino]pentanedioic acid corresponding to the molecular formula $C_{44}H_{62}N_6O_{17}$. It has a relative molecular mass of 947 g/mol and the following structure:

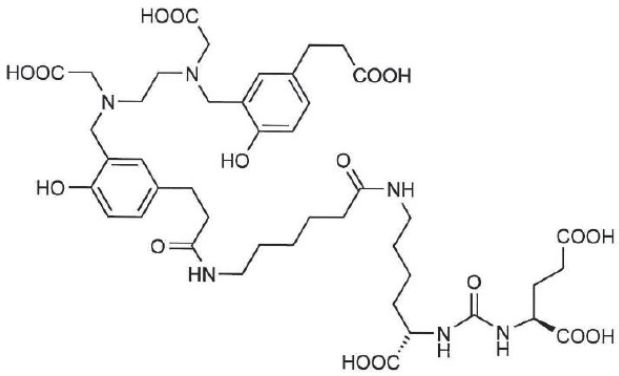


Figure 1: Active substance structure

The chemical structure gozetotide (PSMA-11) was elucidated by suitable tests and they have been adequately described.

Gozetotide (PSMA-11) is a non hygroscopic white to slightly coloured powder, soluble in water and acetonitrile.

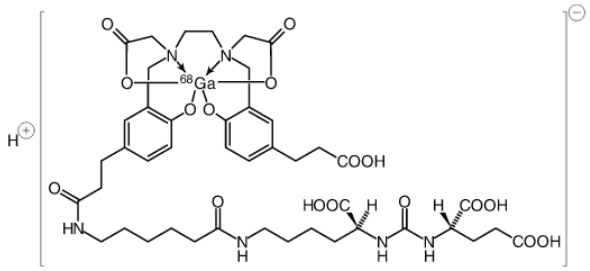
Specific optical rotation: $[\alpha]D_{20}$ = 4.8° .

Polymorphism has not been observed for the active substance.

Note:

The clinical relevant active substance is the with gallium-68 radiolabelled Gozetotide (PSMA-11) obtained by the user after the radiolabelling step of the kit with gallium-68:

[^{68}Ga]Gallium-gozetotide ([^{68}Ga]Gallium-PSMA-11)



"Structure see Ph. Eur. Monograph no. 3044 "[68Ga]Gallium-PSMA-11 Injection"

$C_{44}H_{59}{}^{68}GaN_6O_{17}$

Manufacture, characterisation and process controls

Gozetotide (PSMA-11) is manufactured by one manufacturer.

Detailed information on the manufacturing has been provided in the restricted part of the ASMF and it was considered satisfactory.

Gozetotide is synthesized in 5 main steps: synthesis of PSMA building block, solid phase peptide synthesis including HBED-CC -ligand coupling, cleavage from solid support, deprotection and isolation of crude peptide, chromatographic purification and filtration and final lyophilization using well defined starting materials with acceptable specifications.

During the whole manufacturing process, the formation and purge of product related impurities such as by-products of the synthesis, unreacted starting materials, or degradation products is monitored by analytical RP-HPLC and MS in the course of several in-process control

(IPC) steps. RP-HPLC as well as MS are adequate analytical methods to detect product related impurities.

Limits for the Class II solvents acetonitrile, dimethylformamide, and dichloromethane are defined according to the respective Ph. Eur. general monograph for chemical precursors for radiopharmaceutical preparations 2902 (class 2 solvents ≤ 0.5 %)

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

Specification

Gozetotide (PSMA-11) specification includes tests for appearance (visual), identification (IR, MS), assay (peptide content, net peptide content), impurities (RP-HPLC, GC-MS), residual organic solvents (GC), counter ion content TFA (IC or GC), water content (GC), bacterial endotoxins (Ph. Eur.), microbial contamination/bioburden (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

During the assessment the CHMP requested as Major Objection (MO) that the impurity specifications of the active substance gozetotide should be justified or should otherwise reduce the specification limits for impurities. The impurity specifications were justified by the applicant and this was considered satisfactory.

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

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 5 batches of gozetotide (PSMA-11) from the manufacturer stored in the intended commercial package for up to 36 months (1 batch) and 24 months (4 batches) under long term conditions (-20 ± 5°C) and for up to 24 months under accelerated conditions (+5 ± 3°C), according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, identity, mass spectrometry, counter ion content TFA, water content, net peptide content, peptide related substances/impurities, bacterial endotoxins and microbial contamination/bioburden.

No significant changes in the quality of the chemical precursor are detected under long-term and accelerated conditions.

A temperature excursion study in one batch is performed to evaluate the identified critical stability parameters of the active substance under ICH storage conditions of +25 ± 2°C and 60± 5% RH). The appearance, identity and purity of the peptide, as well as the water content are monitored. Results indicate that under storage conditions of +25 °C ± 2°C over a period of 30 days no significant changes occur in the quality of the active substance.

According to the ICH guideline Q1B, a photostability study is performed in one batch. Based on the results of the study the active substance is photolabile and is to be stored protected from light.

To determine the stability under various stressing conditions (stability in acidic, basic, oxidative, and oxidative-basic solutions), an accelerated aging study is performed in one batch. Results show that it remains within specification at acidic conditions for at least 48 hours. The product is unstable under basic, oxidative and oxidative basic conditions.

The stability results indicate that gozetotide (PSMA-11) manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months stored at -20°C ± 5°C and protected from light in the proposed container.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a sterile white lyophilised powder presented as a kit for radiopharmaceutical preparation.

The physico-chemical properties of PSMA-11 have been considered when choosing the manufacturing process for the powder vial in order to achieve the intended dosage form. Being the solubility of the PSMA-11 with water determined by the active substance manufacturer and being the active substance intended to be directly dissolved in aqueous solution and at much lower concentration than those investigated by the active substance manufacturer, no additional physico-chemical characterization of the active substance was performed for the purpose of the finished product development.

The compatibility of the active substance with the excipients used in the finished product has been demonstrated through the development studies during the selection of suitable excipients for this dosage form, and has been confirmed later by batch analyses and the stability data.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except gentisic acid which complies with "In House" specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The proposed commercial finished product was developed as a sterile lyophilized powder formulation provided in a 1-vial kit. The finished product was developed as a multidose product to be used in combination with a solution of gallium-68 in diluted hydrochloric acid provided by a ^{68}Ge/68Ga radionuclide generator to obtain ^{68}Ga-PSMA-11 solution for injection, being the kit prepared radiolabelled imaging product for intravenous administration.

The compatibility of the kit was tested using two commercially available ^{68}Ge/^{68}Ga radionuclide generators. Both generators are currently approved radionuclide generators in the EU/EEA.

The powder for solution for injection has proved to be compatible for reconstitution and radiolabelling with Gallium [^{68}Ga] in diluted hydrochloric acid solutions, and is therefore kept constant, irrespectively which of both as suitable proven radionuclide of the generator is used.

Both in the SmPC described radionuclide generators are pharmaceutical grade generators with own marketing authorisations in the EU/EEA providing the eluate compliant with the current Ph. Eur. Monograph (2464) for "Gallium Chloride (68Ga) Solution for Radiolabelling". In the case that in the future additional ^{68}Ge/^{68}Ga radionuclide generators possessing their own marketing authorisation are available the suitability of Gallium Chloride (^{68}Ga) Solution for Radiolabelling deriving from these new radionuclide generators with the kit Locametz should be demonstrated before these new radionuclide generators are added to the SmPC of Locametz by a variation procedure.

The formulation development has been performed with the aim of identifying the reaction mixture composition able to allow a simple radiolabelling of PSMA-11 with Gallium-68 by metal - complexation with the eluate from commercially available ^{68}Ge/^{68}Ga generators without any processing of the eluate or any additional purification step.

The development work includes the relevant studies performed for the selection of the active ingredient amount and appropriate excipients and their suitable quantities. The applicant used as reference when selecting the active substance amount, the draft Ph. Eur. Monograph (3044) for "Gallium (68Ga) PSMA-11 Injection" which prescribes for the active ingredient PSMA-11 an amount of not more than 30 µg.

Following the Ph. Eur. recommendation, preliminary tests were conducted using different quantities s of PSMA 11 without exceeding 30 µg as recommended by Ph. Eur. in order to confirm what is the suitable active substance quantity sufficient to obtain ^{68}Ga-PSMA-11 solution with high radiochemical purity in consistent way. 25 µg was selected as final PSMA-11 amount to ensure a margin around the target value still falling within the range of proven radiolabelling efficiency, without exceeding the limit prescribed by the reference Ph. Eur. Monograph.

During the very early development stages, the radiolabelling procedure parameters regarding the reaction time and temperature were defined based on well-known conditions described in literature.
The testing results demonstrated the radiolabelling procedure is robust and the radiolabelled imaging product is stable providing results fully compliant with the proposed quality specification.

Because of the short shelf – life of Ga-68 radiolabelled products of only few hours Ga-68 radiopharmaceuticals are typically radiolabelled at the nuclear medicine department. With the ^{68}Ge/^{68}Ga radionuclide generators a 24 hours / 7 days source of the radionuclide precursor Ga-68 chloride solution for radiolabelling is available in the nuclear medicine departments. The most convenient way for the user to obtain a Ga-68 radiolabelled medicinal product is a "one pot" and "one step" reaction where the Ga-68 chloride solution for radiolabelling is added to a vial containing all components to obtain directly without additional manufacturing steps a ready to use solution for injection in a quality in compliance with the corresponding pharmacopeia monograph without further purification steps.

Therefore, a manufacturing process was developed leading to a lyophilizate powder containing the cold chemical precursor PSMA-11 together with suitable excipients filled as sterile product in a vial which forms after addition of the Ga-68 chloride solution for radiolabelling the ready to use solution for injection.

The necessary manufacturing process of the lyophilizate involves the preparation of an aqueous bulk solution containing the cold precursor PSMA-11 and the excipients which is sterilised by filtration, dispensed in single sterile product vials where the solution is lyophilised under sterile conditions. This manufacturing process is not specific for radiopharmaceuticals and common methods of pharmaceutical technology are used.
It was developed a container closure system which can not only protect the lyophilizate during the shelf-life period but tolerate the radiolabelling reaction of PSMA-11 with Ga-68 chloride solution too. The primary packaging is type I Plus glass vial closed with a rubber stopper and sealed with a flip-off cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.
The manufacturing process consists of 6 main steps: solution compounding, sterile filtration, aseptic filling and partially stoppering of vials, lyophilization, sealing of vials, and visual inspection, labelling and packaging. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process (sterile filtration, filter integrity, bacterial viability, bacterial retention, aseptic filling, lyophilisation, sealing of the vials, sterilization of container closure system and holding times) have been validated using three full-scale production batches which have been processed in the same manufacturing facilities, using the same process and the same equipment as for the batches intended for commercial supply. All three batches fully met the quality control specifications. With the in-process data and the additional testing it has been demonstrated that the manufacturing process is

robust and consistently yields product capable of meeting the pre-defined quality characteristics. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance of the lyophilisate (visual), container closure integrity (visual), reconstitution time (visual), appearance of the reconstitution solution (visual), sub-visible particles (Ph. Eur.), uniformity of dosage units (mass variation) (Ph. Eur.), residual moisture (water content) (KF), pH (pH meter), PSMA-11 assay (HPLC), PMSA-11 identification (HPLC-UV-DAD), gentisic acid assay (HPLC), gentisic acid identification (HPLC), related substance (HPLC), sterility (Ph. Eur.), and bacterial endotoxins (HPLC).

For radiolabelled product: appearance of ^{68}Ga-PSMA-11 solution (visual), pH of ^{68}Ga-PSMA-11 solution (pH meter), radiochemical purity ^{68}Ga-PSMA-11 (sum of two isomers) (HPLC), radiochemical purity: free ^{68}Ga (HPLC), and radiochemical purity: ^{68}Ga non-complexed specie (TLC).

There are no specified identified or specified unidentified degradation products based on forced degradation studies performed on the finished product. Any unspecified degradation product detected in the finished product is controlled with limit of not more than 1.0% as per ICH Q3B (R2) guideline. As described in the Ph. Eur. Monograph for Gallium (68Ga) PSMA-11 injection (3044), the radiochemical impurities are assessed into radiolabelled finished product.

According to the guideline for elemental impurities (ICH Q3D) elemental impurities may arise from several sources. Elemental impurities can be excluded as no metal catalysts are used. Results from validation batches showed that all elemental metals potentially present are far below the allowed limits of 100 ppm/metal impurity. Summarizing all data and information for metals it is concluded that no significant amount of heavy metals is present. Therefore, it is not considered necessary to test for heavy metals on a regular basis.

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

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

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 12 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Stability data was also provided from 3 commercial batches stored for up 12 months under refrigerated conditions at 5 ± 3°C to evaluate if temperatures lower than normal storage temperature could cause changes in chemical/radiochemical or physical aspects for radiopharmaceutical preparation and at 30 ± 2°C / 75% RH ± 5% RH to prove that the finished product is stable throughout its shelf-life storing at 30 ± 2°C.

Samples were tested for appearance of the lyophilisate, container closure integrity, reconstitution time, appearance of the reconstitution solution, sub-visible particles, uniformity of dosage units (mass variation), residual moisture (water content), pH, PSMA-11 assay, PMSA-11 identification, gentisic acid assay, gentisic acid identification, related substance, sterility, and bacterial endotoxins.

For radiolabelled product, samples were tested for appearance of ^{68}Ga-PSMA-11 solution, pH of ^{68}Ga-PSMA-11 solution, radiochemical purity ^{68}Ga-PSMA-11 (sum of two isomers), radiochemical purity, free Ga-68, and radiochemical purity, andGa-68 non-complexed specie.

The analytical procedures used are stability indicating.

All chemical and physical data generated under aforementioned stability conditions meet specifications and therefore, the data demonstrate good stability profile for the finished product.

In-use stability of the radiolabelled finished product was assessed during a study conducted on the three batches at room temperature up to 6 hours. Full physical and chemical product testing was conducted, initially and after 6 hours. The same validated and stability-indicating methods routinely employed during the long-term stability studies were used. No significant changes were observed in any of the physical and chemical parameters and all remained within specification, thus demonstrating 6 hours in-use stability of the radiolabelled imaging product.

A multipiercing in-use stability study was performed on three validation batches at room temperature up to 6 hours in order to support the suitability of the finished product kit for radiopharmaceutical preparation for being a multidose product. No significant changes were observed in any of the physical, chemical and microbiological parameters tested. All tested parameters remained within specification, thus demonstrating the suitability of the kit for radiopharmaceutical preparation, for being a multidose product.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. All results complied with the specifications. The results of photostability study demonstrated that light exposure does not result in unacceptable change in chemical and physical characteristics.

Based on available stability data, the proposed shelf-life of 1 year (unopened) stored bellow 25°C as stated in the SmPC (section 6.3) are acceptable.

After reconstitution and radiolabelling, chemical and physical in-use stability have been demonstrated for 6 hours at 30°C. Store upright.

From a microbiological point of view, unless the method of opening, reconstitution, radiolabelling, or dilution precludes the risk of microbial contamination, the product should be used immediately.

Adventitious agents

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

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

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

One MO had been raised about that the impurity specifications of the active substance gozetotide should be justified or should otherwise reduce the specification limits of impurities. The impurity specifications were justified by the applicant, and this was considered satisfactory. Overall, during the procedure the information of the dossier has been updated and improved as requested.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

PSMA is a type II transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II or N-Acetyl-L-aspartyl-L-glutamate peptidase (NAALADase), and has been confirmed as a biological target for diagnostic imaging in prostate cancer.

The non-clinical program has been designed according to CHMP Guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018).

Pivotal toxicology and safety pharmacology studies as well as validation of bioanalytical methods were performed in accordance with Good Laboratory Practice (GLP) in test facilities that were part of an EU or an OECD (Organisation for Economic Cooperation and Development) Mutual Acceptance of Data (MAD) GLP monitoring programme.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Based on the submitted literature, the mechanism of action of the radiodiagnostic agent ^{68}Ga-PSMA-11 is two-fold. On the one hand, its PSMA-11 core binds to PSMA with high affinity leading to internalisation through endocytosis and a sustained retention of ^{68}Ga-PSMA-11 within the targeted

cancer cell. The binding affinity of ^{67}Ga-PSMA-11 in PSMA-positive lymph node carcinoma of the prostate cells was found to be in a low nanomolar range (K_i = 12.0±2.8 nM). On the other hand, the positron emission from Ga-68 allows for PET imaging. PSMA-positive PC-3 PIP human prostate cancer cells took up approximately 55-70% ^{68}Ga-PSMA-11, and approximately 10% to 15% of the total added radioactivity was internalised. The uptake of ^{68}Ga-PSMA-11 into PSMA-negative PC-3 flu human prostate cancer cells was lower than 0.5% showing PSMA-specific uptake and internalisation. Similar results were obtained in vivo in a mouse model. Uptake of ^{68}Ga-PSMA-11 in PSMA-positive PC-3 PIP tumours was high, whereas the uptake in PSMA-negative PC-3 flu tumours was not visible in the PET/CT scan of the animals. Most normal tissues did not accumulate radioactivity, except for kidneys, where ^{68}Ga-PSMA-11 was clearly retained at 2 h post-dose.

2.5.2.2. Secondary pharmacodynamic studies

At the concentration of 10 µM, PSMA-11 was found not to interact with a panel of 87 potential different targets (receptors, ion channels, enzymes and transporters). This concentration is 1000-fold higher than the theoretical clinical C_{max} of PSMA-11 in patients after a single administration of microdose of 25 µg (Study FR095-0019091). PSMA-11 did not affect cell viability of PSMA-positive (22RV1, prostate cancer) or PSMA-negative (KB, cervical papilloma) human cancer cell lines at the concentrations up to 10 µM suggesting no direct pharmacological activity of the PSMA-moiety itself (Study 0587).

2.5.2.3. Safety pharmacology programme

PSMA-11 at the concentrations of 1, 10 and 100 µM inhibited hERG tail current by 8±4%, 15±4%, and 17±5%, respectively as assessed in stably transfected HEK-293 cells utilising a patch-clamp technique. Given the theoretical clinical C_{max} of 10 nM (the highest assay concentration is 10000-fold higher), no clinically relevant hERG blockade is expected.

In vivo GLP safety pharmacology studies were performed in rats and minipigs. As has been shown by Rovenska et al. (2008), PSMA target is expressed in rats, minipigs and humans, is highly conserved and has similar enzymatic activity in these species. Therefore, rats and minipigs are considered pharmacologically relevant species. PSMA-11 had no effect on general behaviour parameters (Irwin test) in male Sprague-Dawley rats after single intravenous administration at doses of 0, 0.08, 0.25 and 0.75 mg/kg (N = 5 for each group). Intravenous PSMA-11 did not influence respiratory function of the conscious male Sprague-Dawley rats at doses of 0, 0.08, 0.25 and 0.75 mg/kg (N = 8 per group). No effects on cardiovascular system were observed in conscious telemetered minipigs at doses of 0, 0.03, 0.09 and 0.29 mg/kg (N = 2, 4, 6, 8, respectively).

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted, as gallium gozetotide is highly specific and selective for PSMA and PSMA shows overexpression in prostate cancer (see discussion on non-clinical aspects).

2.5.3. Pharmacokinetics

- ***Methods of analysis***

The analytical methods for quantification of PSMA-11 in vehicle by LC-UV, in Tyrode's solution by HPLC-UV and in rat plasma by LC-MS/MS were developed and validated under GLP conditions.

• ***Absorption***

The classical pharmacokinetics of PSMA-11 was investigated in a toxicokinetic study as a part of the GLP extended single dose toxicity study in rats.

• ***Distribution***

The *in vitro* plasma protein binding of PSMA-11 to plasma of various species is moderate (33% for human, 36–44% for rat, and 38–41% for minipig plasma). PSMA-11 did not preferentially distribute to red blood cells as the mean blood-to-plasma ratios for PSMA-11 were below 1 (0.54 for mouse, 0.43 for rat, 0.71 for minipig and human). ^{68}Ga-PSMA-11 injected intravenously in mice was quickly eliminated from the blood, resulting in very high tumour-to-blood ratios after 2 h. Therefore, the accumulation of radioactivity in PSMA-positive PC-3 PIP tumours was high. In contrast, the uptake in the PSMA-negative PC-3 flu tumours was approximately 300-fold lower. The radioactivity level was low in most normal tissues, except kidneys where radioactivity was retained 2 h post-dose. Even at this timepoint tumour-to-kidney ratio was clearly below 1.

• ***Metabolism***

PSMA-11 is metabolically stable in human, rat and minipig plasma (for 2 h) and in liver and kidney S9 fractions (for 60 min) of the same species at physiological temperature. The non-radioactive ^{nat}Ga-PSMA-11 was found to be stable in human, mouse, rat and minipig plasma up to 24 h at 37 °C.

• ***Excretion***

Tissue biodistribution studies in a mouse model revealed renal excretion as a primary elimination route, which is consistent with clinical data.

• ***Pharmacokinetic drug interactions***

In vitro studies of PSMA-11 potential to inhibit cytochrome P450 enzymes in human liver microsomes revealed that PSMA-11 is not a reversible or time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4, as the IC_{50} values could not be determined.

In vitro experiments indicated that PSMA-11 induced CYP1A2, 2B6 and 3A4 metabolic activity with the EC_{50} values of 1.58, 46.4 and 15.4 µg/mL, respectively. This corresponds to 1.67, 49.0 and 16.26 µM, which exceeds the theoretical clinical C_{max} of 10 nM more than 150-fold. Therefore, no clinical relevance is expected.

In vitro drug interaction studies with transporters showed that PSMA-11 is not an inhibitor of P-gp, BCRP, BSEP, MATE1, MATE2-K, OCT1, OCT2, OAT1, OAT3, OATP1B1, and OATP1B3. PSMA-11 was found to be not a substrate of P-gp, BCRP, MATE1, MATE2-K, OCT2, OAT1, and OAT3.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

The toxicology of the unlabelled PSMA-11 was assessed in an extended GLP-compliant single bolus intravenous dose toxicity study in male and female rats (SD) including an observation period of 1 day (10M + 10F) or 2 weeks (5M + 5F), at doses of 0, 0.67 and 1.33 mg/kg.

No mortalities occurred during the extended single dose toxicity study of unlabelled PSMA-11 in rats. Some statistically significant changes in haematological and biochemical parameters occurred within the study duration in the high dose groups (mainly in males) and were still present on day 15. These

changes did not correlate with histopathological changes, were not dose-related and not consistent between sexes. These findings are considered of limited relevance for the clinical situation.

Organ weights of liver, kidney, brain and testes were still higher compared to the control on day 15 at the highest dose tested. Microscopically, minimal, multifocal inflammatory cell foci were seen in the liver, and minimal hyaline casts in the cortex of the kidney, in males and females. Since these findings were already present in the control group, these changes are not considered adverse.

Remarkable were the changes at the injection site on day 2. Preferable male animals exhibited chronic inflammation, mainly characterised by the presence of mononuclear cells (lymphocytes, macrophages, and plasma cells) and accompanied by necrosis. On day 15 only one high-dosed female animal exhibited thrombosis as adverse reactions at the injection site.

The extended single dose toxicity study revealed a NOAEL of 1.33 mg/kg that corresponds to a safety factor of 530 based on body surface area which is in accordance with the appropriate guidelines.

2.5.4.2. Repeat dose toxicity

No repeat-dose toxicity studies with ^{68}Ga-PSMA-11 or the PSMA-11 precursor were submitted (see discussion on non-clinical aspects).

2.5.4.3. Genotoxicity

No genotoxicity studies were performed (see discussion on non-clinical aspects).

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been conducted with ^{68}Ga-PSMA-11 or the PSMA-11 precursor.

2.5.4.5. Reproductive and developmental toxicity

No reproductive and developmental toxicity studies have been conducted with ^{68}Ga-PSMA-11 or the PSMA-11 precursor.

2.5.4.6. Toxicokinetic data

The toxicokinetic analysis demonstrated that PSMA-11 toxicokinetics was similar in males and females, with systemic exposure and peak plasma concentrations increasing with the dose level.

2.5.4.7. Local Tolerance

No specific local tolerance studies have been conducted with ^{68}Ga-PSMA-11 or the PSMA-11 precursor. However, examination of the injection site was included in the extended single dose toxicity study in the rat.

2.5.4.8. Other toxicity studies

No toxicological qualification of drug substance related impurities of degradation products was performed, which is acceptable given the fact that PSMA-11 is a peptide and having in mind that the

max. specified single impurity level is 2% which in this case is far below the TTC for mutagenic impurities and acceptable for a product usually used as single dose.

In silico SAR evaluation of PSMA-11 was performed with a rule-based and a statistical-based prediction software and did not predict any potential mutagenic structures in PSMA-11.

2.5.5. Ecotoxicity/environmental risk assessment

An ERA Phase I for the active ingredient Gozetotide/^{68}Ga-PSMA-11 was provided.

Regarding the PBT assessment, the provided literature is not acceptable as substitute for a logK_{ow} study. Nevertheless, a new study is not deemed necessary, as a logK_{ow} above the threshold value for a PBT assessment is highly unlikely and the most environmentally relevant property of ^{68}Ga-PSMA-11 is its radioactivity, which is already addressed in the SPC.

The PEC*surfacewater* calculation represents an unrealistic worst-case as the treatment regime was not considered. Assuming one treatment per year the PEC*surfacewater* can be reduced by 1/365 resulting in 3.4×10^{-7} µg/L. Consequently, it can be confirmed that a Phase II assessment is not necessary.

Summary of main study results

Substance (INN/Invented Name): Gozetotide			
CAS-number (if available): 1366302-52-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	literature	<4.5	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (treatment regime)	3.4×10^{-7}	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)	^{68}Ga-PSMA-11 is radioactive		(Y)

2.5.6. Discussion on non-clinical aspects

Pharmacodynamics

PSMA is highly expressed in prostate cancer in contrast to other tissues. ^{68}Ga-PSMA-11 is a diagnostic radiopharmaceutical for PET imaging of prostate cancer lesions. Its mechanism of action relies on high affinity binding to PSMA and on positron emission from radioactive Ga-68, which enables PET imaging. ^{68}Ga-PSMA-11 was shown to specifically accumulate in PSMA-positive prostate cancer cells in vitro and in PSMA-positive tumours in vivo. Accumulation in other organs in a mouse model was low except for kidneys. PSMA-11 exhibited no off-target activity further confirming its high selectivity for PSMA. Unlabelled PSMA-11 was not cytotoxic in PSMA-positive and PSMA-negative cells suggesting no pharmacological activity of the peptide itself. PSMA-11 did not inhibit hERG tail current in vitro and had no effects on central nervous, cardiovascular and respiratory systems in rats and minipigs ~~that are~~

~~considered pharmacologically relevant models.~~

No pharmacodynamic drug interaction studies were conducted, which is considered acceptable, as gallium (^{68}Ga) gozetotide is highly specific and selective for PSMA and PSMA shows overexpression in prostate cancer.

Pharmacokinetics

The analytical methods for quantification of PSMA-11 in vehicle by LC-UV, in Tyrode's solution by HPLC-UV and in rat plasma by LC-MS/MS are considered acceptable. For the methods to determine PSMA-11 content in vehicle and Tyrode's solution, linearity was shown in a narrower concentration range than the quantification range of the method. The *in vitro* plasma protein binding of PSMA-11 was moderate. PSMA-11 did not preferentially distribute to red blood cells as the mean blood-to-plasma ratios for PSMA-11 were below 1. After intravenous administration, ^{68}Ga-PSMA-11 quickly accumulated within PSMA-positive PC-3 PIP tumours but not in PSMA-negative PC-3 flu tumours in mice. The radioactivity level was low in most normal tissues, except kidneys where radioactivity was retained 2 h post-dose. Even at this timepoint, tumour-to-kidney ratio was clearly below 1. The applicant explains that high kidney concentrations (higher than tumour concentrations) of [^{68}Ga]Ga-PSMA-11 could be expected, due to the high expression of PSMA and the fact that kidneys are the primary route of excretion of [^{68}Ga]Ga-PSMA-11.Nevertheless, the diagnostic characteristics of [^{68}Ga]Ga-PSMA-11 (short half-life and no emission of DNA-reactive beta particles) limit the safety implications for exposed tissues including the kidney. In addition, no indications of renal toxicity were observed in either the preclinical single dose toxicity study or the adverse event profile (see Clinical safety). The distribution study in a mouse model revealed renal excretion as a primary elimination route. PSMA-11 was metabolically stable in human, rat and minipig plasma and in liver and kidney S9 fractions of these species. PSMA-11 is not a reversible or time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. PSMA-11 slightly induced CYP1A2, 2B6 and 3A4 metabolic activity but not to a clinically relevant extent. The experimental setting was not in line with the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**). One batch of hepatocytes from different donors, i.e. a mixture of hepatocytes from different donors, was used, although the guideline specifies that the induction results should be evaluated separately for each donor. The applicant argues that, despite using a mixture of hepatocytes from different donors, the results of the positive controls indicate that assay sensitivity and performance were sufficient. Although the assessors consider the mixing of donors not an ideal test setup, it is agreed that the response of the positive controls is sufficiently high in this situation to accept it. Overall, PSMA-11 is not a substrate, inhibitor or inducer of cytochrome P450 enzymes. PSMA-11 is not an inhibitor of P-gp, BCRP, BSEP, MATE1, MATE2-K, OCT1, OCT2, OAT1, OAT3, OATP1B1, and OATP1B3. PSMA-11 was found to be not a substrate of P-gp, BCRP, MATE1, MATE2-K, OCT2, OAT1, and OAT3 (see SmPC section 5.2). It was not investigated whether PSMA-11 is a substrate of OCT1, OATP1B1, and OATP1B3, but this is acceptable given primarily renal elimination of the drug. In conclusion, based on the *in vitro* interaction studies, PSMA-11 is not expected to have any clinically significant interaction with other medicinal products (see SmPC section 4.5).

Toxicology

The extended single dose toxicity study of unlabelled PSMA-11 in rats showed that the test item was well tolerated. Statistically significant changes were noted in terms of haematological and biochemical parameters. However, these changes were rather incidental than adverse. All animals (test and control) exhibited chronic inflammation at the injection site. Since only one female animal of the high dose group showed thrombosis at the injection site at the end of the recovery period changes are considered not relevant for the clinical setting. This highest dose tested provides a safety margin based on body surface area conversion of approximately 530-fold relative to the potential maximum human

mass dose (25 µg) in a 1.7 m^2 patient.

No genotoxicity, carcinogenicity and long-term repeat-dose toxicity studies have been conducted with ^{68}Ga-PSMA-11 or the PSMA-11 precursor as they are not required for this type of radioactive oncology diagnostic product according to the appropriate guidelines: CHMP Guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018) and Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations (Guideline for Industry, FDA August 2018), repeat-dose toxicity studies are not required for a microdose radiodiagnostic. For PSMA-11, the non-radioactive part of ^{68}Ga-PSMA-11, a structure-activity alert relationship (SAR) evaluation for bacterial mutagenicity did not find any alert for potential mutagenic structural features in PSMA-11.

No reproductive and developmental toxicity studies have been conducted with ^{68}Ga-PSMA-11 or the PSMA-11 precursor as they are not required according to the relevant guidelines (EMA/CHMP/SWP/686140/2018).

Section 4.6 of the SmPC reflects that Locametz is not indicated for use in females. There are no data on the use of gallium (^{68}Ga) gozetotide in females, or on the effects on the breast-fed newborn/infant or on milk production, and on human fertility.

Radiation has the potential to induce mutagenic effects on gonads and germ cells. The binding and internalization of ^{68}Ga-PSMA-11 at the level of the prostate could theoretically lead to DNA damage during spermatogenesis and impairment of male fertility or effects on embryofoetal development. However, the testes radiation exposure after a [^{68}Ga]Ga-PSMA-11 scan is expected to be 52-fold lower than the threshold of temporary infertility of 150 mGy. Therefore, no effects on spermatogenesis and male fertility are expected.

Conclusions on ERA

Locametz PEC $_{surfacewater}$ value is below the action limit of 0.01 µg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5. Therefore, it is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Locametz is a radiodiagnostic agent for localisation of PSMA-positive prostate cancer lesionsby PET imaging. Gozetotide was evaluated in safety pharmacology and single dose toxicity studies. Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology and single dose toxicity. Mutagenicity studies and carcinogenicity studies have not been carried out with gallium (^{68}Ga) gozetotide. This is in accordance with the relevant guidelines. In conclusion, the non-clinical pharmacology, pharmacokinetics and toxicology have been adequately characterised *in vitro* and *in vivo*.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

The applicant has submitted two study reports (one from clinical study VISION – PSMA-617-01 study - and one from reviewer variability study based on the VISION data) and more than 20 published studies to support the claims on diagnostic performance, technical performance, impact on patient management, inter-reader variability and safety (reference is made to sections Clinical efficacy and Clinical safety). Biodistribution and radiation dosimetry are substantiated with 5 published studies and retrospective analysis of the raw data collected in one study (Sandgren et al.). Further published literature has been provided to present PK and PD. Additionally, non-clinical tests to evaluate metabolism, potential for drug-drug interactions, and for QT effects were performed and are being discussed in the non-clinical part of this assessment.

Tabular overviews of submitted published studies are presented in different sections of this report. Tabular listing of clinical studies and analyses conducted by the Applicant is displayed below.

- **Tabular overview of the Applicant's own clinical data source**

Role **Study or source** **No. of patients**	**Type of study and study title**	**Key study endpoints in support of ^{68}Ga-PSMA-11**
Efficacy and safety [Study PSMA-617-01] (VISION) 1003 patients scanned with ^{68}Ga-PSMA-11 831 randomized to either ^{177}Lu-PSMA-617 + BSC/BSoC or BSC/BSoC alone Ongoing as of 27-Jan-2021	Prospective study International, prospective, open-label, multicenter, randomized Phase III study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive mCRPC, previously treated with 1 to 2 taxane regimens and at least one novel androgen axis drug.	**Efficacy:** Technical performance of ^{68}Ga-PSMA-11. Clinical impact on patient outcome: alternate primary endpoints rPFS and OS for randomized treatment **Safety of ^{68}Ga-PSMA-11:** Exposure Demographics Concomitant medications AEs
Efficacy [Study PSMA-617-01 Reviewer Variability] based on ^{68}Ga-PSMA-11 PET/CT scans from Study PSMA-617-01 125 patients	Retrospective study 3 independent readers performed reads of 125 ^{68}Ga-PSMA-11 PET/CT scans from Study PSMA-617-01 eligibility screening.	Inter-reader agreement of ^{68}Ga-PSMA-11 PET images among 3 independent blinded readers; intra-reader agreement of ^{68}Ga-PSMA-11 PET images within each of 3 independent blinded readers.
Biodistribution and dosimetry Analysis done utilizing raw data collected by Sandgren et al (2019) 6 patients	Retrospective analysis of absorbed doses and effective dose in patients with low-risk prostate cancer	Calculation of radiation absorbed doses after administration of ^{68}Ga-PSMA-11, not reported in the original publication by Sandgren et al., and of effective dose.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

^{68}Ga-PSMA-11 is administered intravenously. Consequently, the absolute bioavailability is 100%.

Biodistribution

The biodistribution and the dosimetry of the radiopharmaceutical ^{68}Ga-PSMA-11 was reported in the following published scientific articles cited by the applicant: Afshar-Oromieh et al 2016 (doi: 10.1007/s00259-016-3419-0), Pfob et al. 2016 (doi: 10.1007/s00259-016-3424-3), Green et al. (doi: 10.1016/j.nucmedbio.2016.11.002), Demirci et al. 2018 (doi:10.1093/rpd/ncy111) and Sandgren et al. 2019 (doi: 10.1186/s40658-018-0239-2). Table below shows a summary of the key-points of the abovementioned studies.

Table 1: Summary of the published studies on biodistribution and dosimetry of ^{68}Ga-PSMA-11

Reference	Num. pat-s Population	Age (years)	Administered Activity, MBq	Data acquisition	Data analysis – dosimetry methods	Resulting dose coefficients
Demirci et al. (2018) Istanbul, Turkey	7 Biopsy proven prostate cancer	67 (57-79)	246 (192-326)	PET/CT 20, 40, 60, 120, 200 min p.i. Top of the head to mid-thigh	Source regions considered: lacrimal glands, parotid, submandibular glands, kidneys, liver, spleen, RBM, urinary bladder contents and body remainder RBM: activity determined from lumbar vertebras (image-based) TAC, TIAC: NUKFIT software Dose calculation: OLINDA/EXM software version 1.0; for lacrimal, parotid and submandibular glands the unit density sphere model in OLINDA/EXM was used Voiding interval: n.a. Effective dose: according to ICRP Publication 60	**Absorbed organ dose:** Kidneys: 0.246 mGy/MBq Lacrimal glands: 0.040 mGy/MBq Salivary glands: 0.096 mGy/MBq Urinary bladder wall: 0.084 mGy/MBq Liver: 0.029 mGy/MBq Spleen: 0.039 mGy/MBq Bone marrow: 0.012 mGy/MBq **Effective dose:** 0.0166 mSv/MBq

Reference	Num. pat-s Population	Age (years)	Administered Activity, MBq	Data acquisition	Data analysis – dosimetry methods	Resulting dose coefficients
Afshar-Oromieh et al. (2016) Heidelberg, Germany	4 Recurrent prostate cancer	68 (62-72)	173 (152-198)	PET/CT 5, 60, 120, 180, 240, 300 min p.i. Whole-body scans	Source regions considered: liver, spleen, kidneys, urinary bladder contents, small intestine, colon, body remainder; Uptake in salivary and lacrimal glands analysed but not explicitly used for dosimetry, uptake in these glands was attributed to body remainder TAC, TIAC: bi-exponential fit (software unknown) Dose calculation: OLINDA/EXM software version 1.1 Voiding interval: n.a. Effective dose: according to ICRP Publication 60	**Absorbed organ dose:** Kidneys: 0.262 mGy/MBq Lacrimal glands: n.a. Salivary glands: n.a. Urinary bladder wall: 0.130 mGy/MBq Liver: 0.031 mGy/MBq Spleen: 0.045 mGy/MBq Bone marrow: 0.009 mGy/MBq **Effective dose:** 0.0236 mSv/MBq
Pfob et al. (2016) Munich, Germany	5 History or high suspicion of prostate cancer	65 (55-71)	140 (120-158) with 20 mg furosemide	PET/MRI 10, 60, 130, 175 min p.i. Skull to mid-thigh	Source regions considered: brain, kidney, liver, lungs, muscle, RBM, spleen, urinary bladder content RBM: activity determined indirectly from blood (blood-based) TAC, TIAC: bi-exponential fit with OLINDA/EXM software version 1.0 Dose calculation: OLINDA/EXM software version 1.0 Voiding interval: voiding after each scan Effective dose: according to ICRP Publication 60	**Absorbed organ dose:** Kidneys: 0.121 mGy/MBq Lacrimal glands: n.a. Salivary glands: n.a. Urinary bladder wall: 0.164 mGy/MBq Liver: 0.021 mGy/MBq Spleen: 0.041 mGy/MBq Bone marrow: 0.008 mGy/MBq **Effective dose:** 0.0158 mSv/MBq
Green et al. (2017) Indianapolis, IN, US	9 Prostate cancer presenting with biochemical failure	Not reported	112.5±3.3	PET/CT 0-10 min p.i. – pelvis (list-mode); 15 min p.i. – pelvis-to-head; 40 min p.i. – prlvis; 60, 90 min p.i. – pelvis-to-head; 115 min p.i. – pelvis Urine samples collected at approx. 40 and 115 min p.i.	Source regions considered: lacrimal glands, parotid and submandibular glands, liver, kidneys, spleen, pancreas, urinary bladder contents TAC, TIAC: n.a. Dose calculation: OLINDA/EXM software version n.a. (probably version 1.0). Not clear how OLINDA/EXM software was employed for source regions lacrimal, parotid and submandibular glands. Voiding: 2 h p.i. Effective dose: n.a., probably according to ICRP Publication 60	**Absorbed organ dose:** Kidneys: 0.413 mGy/MBq Lacrimal glands: n.a. Salivary glands: n.a. Urinary bladder wall: 0.067 mGy/MBq Liver: 0.040 mGy/MBq Spleen: 0.058 mGy/MBq Bone marrow: 0.010 mGy/MBq **Effective dose:** 0.0258 mSv/MBq
Sandgren et al. (2019) Umeå, Sweden	6 Low-risk prostate cancer	68 (62-72)	155 (133-178)	PET/CT 0, 10, 20 min p.i. – head to thigh; 30, 90, 180, 255 min p.i. –	Source regions considered: blood, kidneys, liver, spleen, salivary glands, lacrimal glands, urinary bladder contents and body remainder	**Absorbed organ dose:** Kidneys: 0.240 mGy/MBq Lacrimal gland: 0.110 mGy/MBq Salivary gland: 0.089 mGy/MBq Urinary bladder wall:

Reference	Num. pat-s Population	Age (years)	Administered Activity, MBq	Data acquisition	Data analysis – dosimetry methods	Resulting dose coefficients
				head-to-toe (whole-body). Venous blood samples at 45, 85, 175 and 245 min p.i. Urine samples collected up to 4 h p.i.	TAC, TIAC: SAAM II software to obtain a fit, analytical and numerical integration methods to compute TIACs Dose calculation: IDAC-Dose 2.1; for lacrimal glands sphere module of IDAC-Dose 2.1 was used; Monte Carlo methods used to consider lacrimal glands as a source region Voiding interval: 3.5 h Effective dose: according to ICRP Publication 103	0.057 mGy/MBq Liver: 0.053 mGy/MBq Spleen: 0.046 mGy/MBq Bone marrow: 0.015 mGy/MBq **Effective dose:** 0.022 mSv/MBq

PET: positron emission tomography, CT: computerized tomography, MRI: magnetic resonance imaging, RBM: red bone marrow, TAC: time-activity curve, TIAC: time-integrated activity coefficient

Additionally, the Applicant re-calculated dosimetry from the data of one published study (Sandgren et al.) to provide the full dosimetry dataset. The biodistribution of ^{68}Ga-PSMA-11 was analysed in patients with prostate cancer. The number of patients enrolled in each study ranged from 4 to 9.

The published pharmacokinetic data of ^{68}Ga-PSMA-11 in blood are very limited. Sandgren et al. reported a rapid clearance of ^{68}Ga-PSMA-11 from blood based on the activity measurements in blood samples withdrawn 45–245 min p.i. Sandgren et al. determined a bi-exponential function describing the time-activity curve in blood. It consisted of a fast component at the early time-points post-injection, followed by a slow component with a half-life of 4.4 h. The latter reflected the biologic clearance of ^{68}Ga-PSMA-11 from blood. Radiopharmaceutical ^{68}Ga-PSMA-11 accumulated preferably in kidneys, liver, spleen, salivary glands and lacrimal glands. This was observed consistently by all authors. The uptake in these regions was determined based on PET/CT (or PET/MRI in the study by Pfob et al.) partial- or whole-body scans performed at different time-points after administration (latest time-point at 300 min p.i. in the study by Afshar-Oromieh et al.). Green et al. collected additionally urine samples and Sandgren et al. collected venous blood as well as urine samples to define and quantify the blood clearance and the urinary excretion of ^{68}Ga-PSMA-11. All authors observed that radiopharmaceutical ^{68}Ga-PSMA-11 is primarily excreted via kidney-urinary pathway. Green et al. reported that until approximately 120 minutes post-injection about 14% of administered activity of ^{68}Ga-PSMA-11 was excreted in urine.

Based on the terminal elimination half-life of 4.4 h and considering that the physical half-life of Ga-68 is 68 min, the resulting effective half-life of ^{68}Ga-PSMA-11 is 54 min.

In the absence of a reported Cmax, the highest anticipated injected total peptide concentration in plasma would be 0.01 µg/ml (10 nM) assuming the 25 µg microdose [SBP], a plasma volume of 2.5 L and the molecular weight of PSMA-11 of 947.0 g/mol.

Dosimetry

^{68}Ga-PSMA-11 showed notable uptake in kidneys, liver, spleen and salivary glands. This was consistent within all studies and these organs were considered source regions in dosimetry calculations. Uptake in lacrimal glands was analysed by all authors except Pfob et al. Afshar-Oromieh et al. did not consider salivary and lacrimal glands as distinct source regions and attributed activity of ^{68}Ga-PSMA-11 accumulated in these organs to source region body remainder. All authors confirmed a predominantly renal excretion of ^{68}Ga-PSMA-11 and urinary bladder contents was a source region in dose calculations done by all authors. The assumed voiding intervals / voiding times were not specified in some of the studies. Sandgren et al. also calculated TIAC for blood based on the measured activity of ^{68}Ga-PSMA-11 in blood samples withdrawn up to 245 min p.i. and subsequently used this value in dosimetry.

All studies except the one by Sandgren et al. employed the software OLINDA/EXM for the calculation of absorbed organ dose coefficients. The effective dose coefficients were derived according to the formalism and the tissue weighting factors of the ICRP Publication 60 (1991). Sandgren et al. used the software IDAC-Dose 2.1 for dosimetry and computed the effective dose coefficients with the formalism and tissue weighting factors recommended in the ICRP Publication 103 (2007).

Sandgren et al. additionally applied Monte Carlo methods to include lacrimal glands as a source region in dosimetric calculations.

Initially, the applicant selected the study by Demirci et al. as a key publication. However, methodology utilized by Sandgren et al. was considered more adequate, and replacement of data by Demirci et al. with Sangren et al. was requested by the CHMP.

Tissue dosimetry was similar across studies for ^{68}Ga-PSMA-11 with high levels in kidney, salivary and lacrimal glands, spleen and liver.

Sandgren et al. reported the dose coefficients for a limited number of organs.

The Applicant has gained access to raw data collected by Sandgren et al. and re-calculated all absorbed dose coefficients (for the organs published by the authors and for those missing in the publication) using a methodology similar to the original one described by Sandgren et al. The intermediate results (Time-integrated activity coefficients, organ blood masses, and lacrimal gland S-Value) as published in the Sandgren et al. and received as supplementary data from the sponsor of the study (Umea University), were assumed to be valid, and the recalculation started with these intermediate results.

Approximately 75% of the organ absorbed doses originally reported by Sandgren et al. were reproduced to within ± 5%, and the remaining 25% of the organ absorbed doses were reproduced to within ± 10%. The effective dose was reproduced to within less than 1% of the Sandgren et al. reported value (see below).

Table 2: Dosimetry Results Comparison Sandgren et al. Results vs. Recalculated Results

Median radiation absorbed doses for organs and tissues of adult patients (N=6) following intravenous injection of gallium (^{68}Ga) gozetotide including observed ranges were calculated by Sandgren et al, 2019, using ICRP/ICRU voxel phantom with the software IDAC-Dose 2.1.

Organs Original Sandgren	(mGy/MBq)	Recalculated (mGy/MBq)	Percent Difference
Eye lenses	0.0051	0.0047	-7.3%
Esophagus	0.014	0.014	-3.6%
Left colon wall*	0.014	0.013	-9.3%
Right colon wall*	0.014	0.015	3.6%
Stomach wall	0.015	0.015	-1.3%
Kidneys	0.24	0.24	-0.8%
Lacrimal Glands	0.11	0.11	4.1%
Liver	0.053	0.053	0.2%
Lung	0.016	0.016	0.0%
Red (active) bone marrow	0.015	0.015	0.0%
Endosteum (bone surface)	0.011	0.011	-4.5%
Salivary glands	0.089	0.088	-1.6%
Skin	0.0067	0.0062	-7.6%
Spleen	0.046	0.046	0.2%
Testes	0.0087	0.0081	-7.0%
Thyroid	0.010	0.010	-2.7%
Urinary bladder wall	0.057	0.058	1.9%
Effective dose ICRP 103 [mSv/MBq]	0.022	0.022	0.9%

*Reported in Sandgren et al. as a single value labeled "Colon"
Note1: If the recalculated results are rounded to 2 significant figures, the percent difference between the original Sandgren et al. reported ED, and the recalculated rounded ED becomes 0.0%.

Sensitivity analyses 1) using the TIACs directly as published by Sangren et. al in IDAC-DOSE 2.1, 2) using blood corrected TIACs derived from the published TIACs, 3) using the blood corrected TIACs derived from the supplemental data supplied, 4) using the median values of the reported and blood corrected TIACs, were additionally conducted. All of these methods reproduced the Effective Dose to within ± 5%. All of the methods involving blood correction of the TIACs reproduced the Effective Dose to within ± 2%.

The proposed dosimetry table in the SmPC now includes the effective dose and the absorbed doses for the organs as reported in the peer-reviewed Sandgren et al. publication and newly calculated absorbed doses for the organs not reported in the paper.

Table 3: Dosimetry table as proposed in the SmPC

	Radiation absorbed dose (mGy/MBq)[1]	
	N=6	
Organ	**Median (mGy/MBq)**	**Range (mGy/MBq)**
Adrenals	0.048	0.0405 – 0.0548
Brain	0.008	0.0065 – 0.0079
Breast	0.008	0.0077 – 0.0087
Endosteum (bone surface)*	0.011	0.0095 – 0.0110
Eye lenses*	0.0051	0.0047 – 0.0054
Gallbladder wall	0.027	0.0212 – 0.0343
Heart wall	0.026	0.0236 – 0.0317
Kidneys*	0.240	0.2000 – 0.2800
Lacrimal glands*	0.110	0.0430 – 0.2000
Left colon wall**	0.014	0.0120 – 0.0140
Liver*	0.053	0.0380 – 0.0710
Lungs*	0.016	0.0130 – 0.0170
Muscle	0.0083	0.0073 – 0.0086
Oesophagus*	0.014	0.0110 – 0.0150
Pancreas	0.019	0.0173 – 0.0209
Recto-sigmoid colon wall	0.013	0.0108 – 0.0149
Red (active) bone marrow*	0.015	0.0140 – 0.0150
Right colon wall**	0.014	0.0120 – 0.0140
Salivary glands*	0.089	0.0740 – 0.1500
Skin*	0.007	0.0059 – 0.0069
Small intestine wall	0.014	0.0129 – 0.0149
Spleen*	0.046	0.0300 – 0.1000
Stomach wall*	0.015	0.0150 – 0.0170
Testes*	0.009	0.0074 – 0.0089
Thymus	0.0081	0.0072 – 0.0085
Thyroid*	0.010	0.0090 – 0.0100

Urinary bladder wall*	0.057	0.0280 – 0.0840
Effective dose [mSv/MBq]*[2]	0.022	0.0204 – 0.0242

[*] as reported by Sandgren et al, 2019; all other organ estimates were estimated based on the time-integrated activity coefficients of the source organs published in the paper

** reported in Sandgren as a single value labelled "Colon"

[1] doses were calculated using the software IDAC-Dose 2.1.

[2] derived according to ICRP Publication 103

Two bridging studies in Japanese and Chinese population are currently planned. The gallium (^{68}Ga) gozetotide dosimetry data from the Japanese study (CAAA617A11201) are expected to be available in approximately 4-6 patients in Q3 2024. The gallium (^{68}Ga) gozetotide dosimetry assessments in this study are not mandatory but optional according to the protocol.

The gallium (^{68}Ga) gozetotide dosimetry data from the Chinese study (CAAA617A12201) are expected to be available:

- in approximately 4-6 patients in Q2 2027 (interim results)
- in approximately 4-6 additional patients in Q3 2028 (final results)

Once available, the Applicant will report the results within the PSUR.

Elimination

Results from in vitro metabolism studies showed that ^{68}Ga-PSMA-11 was metabolically stable against the enzymatic degradation by human liver and kidney S9 fraction for up to 1 hour, indicating negligible metabolism in human (see Non-clinical section).

PSMA-11 showed high rates of renal excretion and excretion into the urinary bladder (Pfob et al 2016). Cumulative urinary excretion after 120 minutes post-injection of ^{68}Ga-PSMA-11 accounted for 14% of the administered dose (Green et al 2017). In the studies evaluating dosimetry of ^{68}Ga-PSMA-11 no transfer of activity to alimentary tract was reported.

The inter- and intra-subject variability in ^{68}Ga-PSMA-11 PK, biodistribution, and dosimetry related to the differences in the formulation was not assessed.

Dose proportionality and time dependencies

No data were provided. ^{68}Ga-PSMA-11 is dosed based on MBq/kg body weight, therefore, the administered dose/radioactivity depends on the body weight.

Special populations

Studies in special populations have not been submitted. Subgroup analyses to test the possible effects of intrinsic and extrinsic factors on safety were performed on the data in PSMA-617-01 clinical studies and did not reveal considerable effects (refer to section Clinical safety).

Given the low micro-dose, fast elimination and short effective half-life of less than an hour, renal impairment was regarded unlikely to have a clinical impact on PK or biodistribution of ^{68}GaPSMA 11

with respect to safety or the imaging performance and no dose adjustment is proposed for patients with renal impairment.

Pharmacokinetic interaction studies

No clinical drug-drug interaction studies were submitted. ^{68}Ga-PSMA-11 is a single, microdose administration exerting no pharmacological effect, and a short biological half-life which suggests the risk for drug-drug interactions is minimal.

In vitro metabolism and interaction studies with transporters and plasma protein binding measurements performed on ^{68}Ga–SMA-11 indicate that the compound has a very low risk for clinically relevant drug-drug interactions.

Pharmacokinetics using human biomaterials

Please refer to section on non-clinical aspects.

Different formulations and bridging

The proposed commercial formulation of the product was not tested in a clinical study and differs from the 11 formulations of ^{68}Ga-PSMA-11 applied in the single clinical trial conducted by the Applicant (Study PSMA-617-01), as well as in the studies from published literature. No bioequivalence or bridging studies were provided.

pH and osmolality

The range of pH of the commercial parenteral solution and the PSMA-617-01 study formulations differ. The targeted pH specification is in line with the pH of another authorized diagnostic medicinal productNo direct comparison between the proposed commercial formulation (AAA) and the formulations used in the PSMA-617-01 study was performed, as no osmolality result was available for the formulations used in the PSMA-617-01 study. The estimated osmolality of ^{68}Ga-Locametz is roughly within the range of 600 to 800 mOsm/kg.

Peptide mass

The 25 µg peptide amount in the proposed kit (22.5 - 27.5 µg /vial) is in line with the recommendations of the Ph. Eur. Monograph (3044) for "Gallium (68Ga) PSMA-11 Injection".

Saturation effects at the lesion level is regarded highly unlikely based on the following: An estimated total peptide concentration in plasma (Cmax) is 0.01 µg/mL (10 nM); Experiments in a mouse model showed that a 16-fold excess of PSMA-11 mass, achieved by varying the specific activity of the 100 µCi administration, did not translate into a marked change in tumor uptake (Pillarsetty et al 2016); A 100-fold increase in the mass of co-administered PSMA-11 did not impact the uptake of ^{177}Lu-PSMA-617 in PSMA-positive xenografts (Kalidindi et al 2021).

Kit used in PSMA-617-01 study and proposed commercial formulation

The kit-based process has been used in the PSMA-617-01 study to prepare ^{68}Ga-PSMA-11 doses, in addition to the more commonly used automatic module-based process. It has been shown that automated synthesis module and sterile cold kit for ^{68}Ga-PSMA-11 do not show differences in PET/CT image quality (Calderoni et al 2020).

Differences Compared to Formulations from Literature

No data have been provided.

2.6.2.1. Pharmacodynamics

Mechanism of action

^{68}Ga-PSMA-11 as a radioactive diagnostic agent is designed for molecular imaging and does not exert any pharmacodynamic effect. ^{68}Ga PSMA 11 has high affinity for PSMA, which is usually overexpressed in prostate cancer lesions, in cancerous lymph nodes and other metastases and bone lesions. Competitive cell binding assays determined the binding affinity of ^{67}Ga-PSMA-11 in PSMA positive LNCaP cells to be 12.0 ± 2.8 nM. Biochemical studies revealed the inhibition potency of natGa-PSMA-11, the non-radioactive surrogate, using an enzyme-based NAALADase assay with recombinant human PSMA to be 7.5 ± 2.2 nM (Eder et al 2012).

Cell uptake and internalization studies of ^{68}Ga-PSMA-11 were conducted with PC-3 PIP [+] and [-] flu cells after incubation for 2 and 4 h, respectively. The uptake of ^{68}Ga-PSMA-11 into PSMA-positive PC-3 PIP cells was approximately 55% to 70%, whereas the internalized fraction was about 10% to 15% of total added activity. The uptake dropped to < 0.5% when PSMA-negative PC-3 flu cells were used, which demonstrates PSMA-specific uptake/internalization of ^{68}Ga-PSMA-11 (Umbricht et al 2017).

Primary and Secondary pharmacology

Pharmacodynamical effects of ^{68}Ga-PSMA-11 were reported in multiple published studies. Results from two studies are summarised in this section (Prasad et al. 2016 and Afshar-Oromieh et al. 2013).

Higher median uptake of PSMA ligands in prostate tumours compared to normal prostate was shown by means of calculating standard uptake values (SUV) in various organs and tissues in the patients with PCa by Prasad et al 2016. In this study highest uptake (median/IQR/range) of the tracer was found in the kidneys (49.6/40.7–57.6/2.7–97.0) followed by the submandibular glands (17.3/13.7–21.2/7.5– 30.4), parotid glands (16.1/12.2–19.8/5.5–30.9) and duodenum (13.8/10.5–17.2/5.8–26.9). The best cut-off value for differentiating physiological uptake in the primary tumour from that in the prostate was found to be an SUVmax of 3.2. The median SUVmax in the primary tumour (n=35), locally recurrent PCA (n=8), lymph node (n=166), bone (n=157) and other metastases (n=3) were 10.2, 5.9, 6.2, 7.4 and 3.8, respectively. The best cut-off values for differentiating non-pathological uptake in lymph nodes and bones from tumour uptake were found to be SUVmax of 3.2 and 1.9, respectively. Patients with PSA G2 had significantly lower SUVmax in bone metastases as compared to patients with PSA ≥2 (pG 0.01).

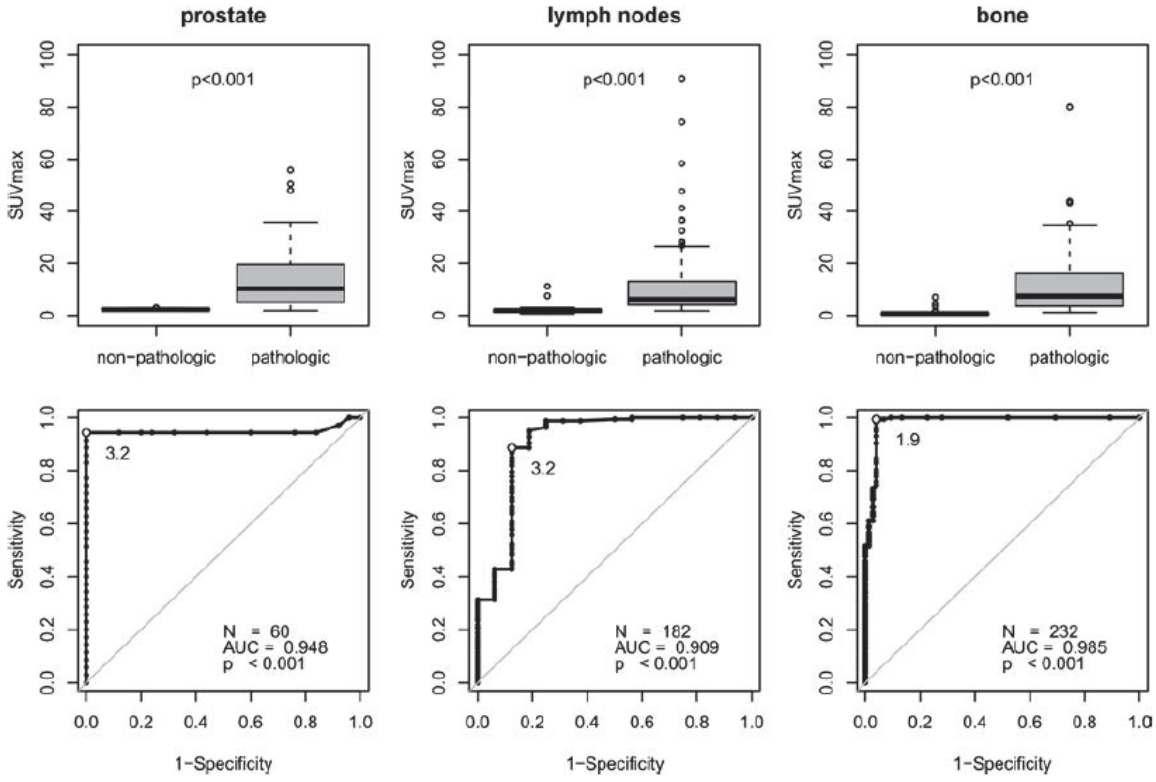


Figure 2: Boxplots (upper row) and ROC analysis (lower row) of pathological vs. non-pathological uptake in the prostate, lymph nodes and bone

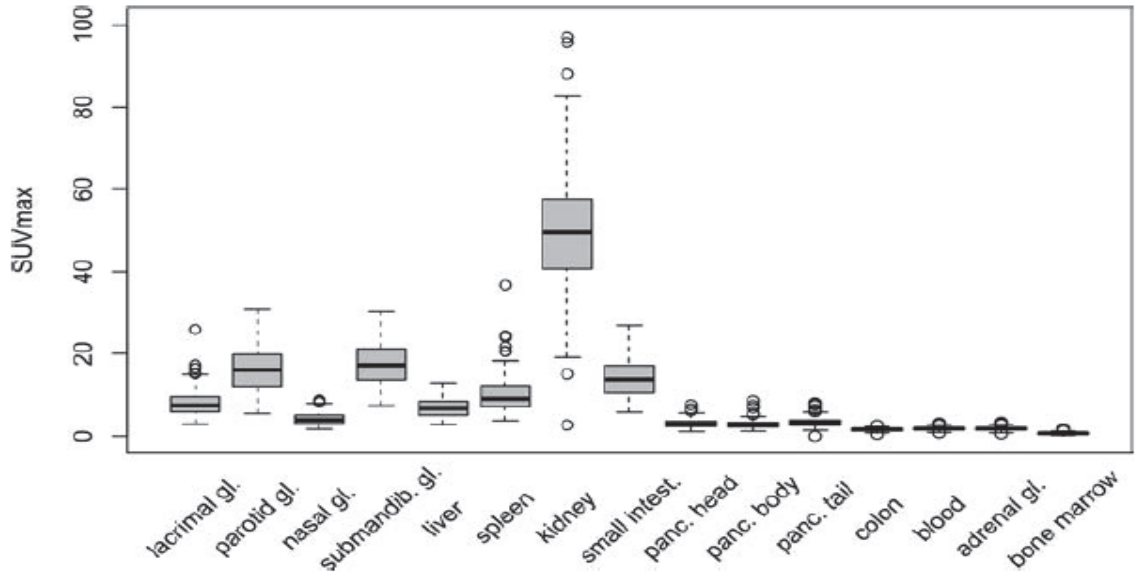
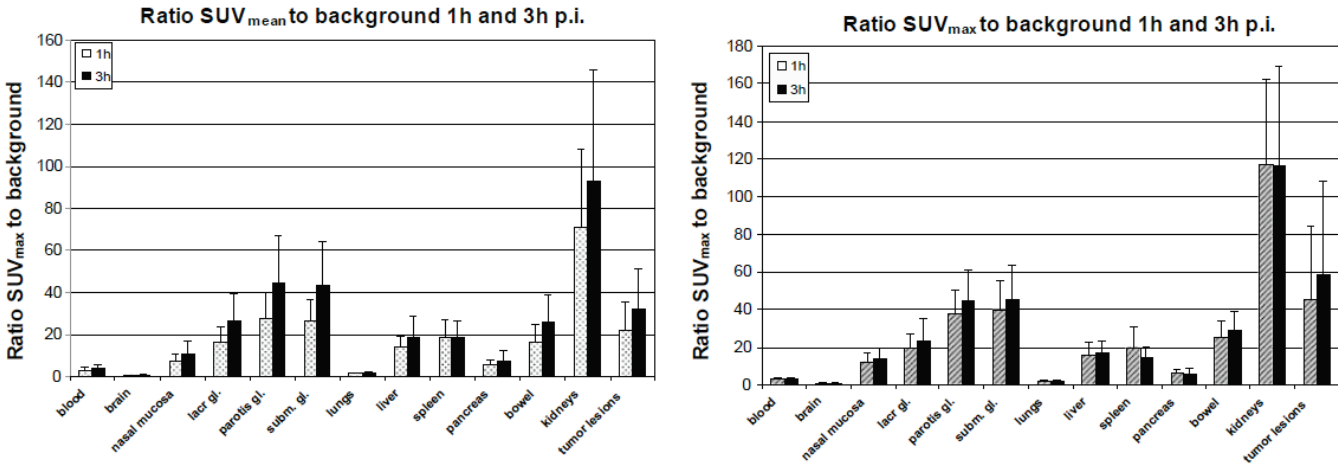


Figure 3 Update of Ga-PSMA-11 in healthy tissues of the patients with PCa

Metastases and recurrent PC, as well as lesions suspicious for prostate carcinoma, presented with excellent contrast at 1 h post injection of ^{68}Ga-PSMA-11 leading to an excellent detection rate of lesions suspicious for cancer even at low PSA levels (Afshar-Oromieh et al 2013). Median tumour to background ratios were 18.8 (2.4–158.3) in early images and 28.3 (2.9–224.0) in late images (after 3 h).

Figure 4: SUVmean and SUVmax ratio to background after 1 and 3 hours from injection of ^{68}Ga-PSMA-11 in patients with PCa



2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

^{68}Ga-PSMA-11 is administered via i.v. injection and its bioavailability is 100%. No food effects have been studied, which is acceptable given the administration route.

Distribution of the substance has been adequately studied and characterised. ^{68}Ga-PSMA-11 is rapidly and extensively distributed with uptake being highest in kidneys, liver, spleen, salivary glands and lacrimal glands. ^{68}Ga-PSMA-11 showed a bi exponential profile in blood consisting of a fast component early time-points (6.5 min) after injection, followed by a slow component with a half-life of 4.4 h. The slow component reflected the biologic clearance of ^{68}Ga-PSMA-11 from blood. The half-life of the fast component estimated by Sandgren et al. is associated with a substantial uncertainty and cannot be well characterised due to a lack of experimental data at the early time-points. Effective half-life of ^{68}Ga-PSMA-11 is 54 min. At 120 min post injection 14% of administered substance was excreted.
In the absence of a reported Cmax, the highest anticipated injected total peptide concentration in plasma would be 0.01 µg/ml (10 nM) assuming the 25 µg microdose, which is low. This is in the same range as the in vitro binding affinity constants for PMSA-11 (7.5-12 nM) (see non-clinical pharmacology) and, therefore, target binding is unlikely to be saturated.
The substance is not metabolised and non-clinical studies did not reveal potential for drug interactions, therefore, no PK drug-drug interaction studies have been conducted, which is agreed.

Kidney is the organ receiving the highest absorbed dose because of the predominantly urinary excretion of ^{68}Ga-PSMA-11 and the physiological expression of PSMA in renal proximal tubules. Three other organs receiving the next highest absorbed doses are lacrimal glands, salivary glands and urinary bladder wall, the latter mainly through the activity of ^{68}Ga-PSMA-11 in urine.

Initially, for dosimetry assessments, the applicant selected the study by Demirci et al. as a key publication. However, there are several limitations that this study carries and study by Sandgren et al. appears more adequate as the "key" source of dosimetry information. This opinion is based on the following:

- Software OLINDA/EXM used by Demirci et al. does not provide absorbed dose coefficients for the complete list of target regions as specified for the current ICRP reference phantoms, in contrast to the

software IDAC-Dose 2.1 used by Sandgren et al. The effective dose coefficients were calculated by Demirci et al. (and all other authors except Sandgren et al.) according to the formalism and the tissue weighting factors of the ICRP Publication 60 (1991). The current recommendations of the ICRP (Publication 103 from 2007) employ a different formalism and updated values of the tissue weighting factors. The effective dose coefficients reported by Sandgren et al. were computed using the new tissue weighting factors from the ICRP Publication 103 (2007). Note that according to the ICRP Publication 103, the effective dose is to be calculated as an average value between men and women. However, ^{68}Ga-PSMA-11 is administered to patients with prostate cancer, and, thus, only one component of the effective dose from ^{68}Ga-PSMA-11 can be calculated – for adult males.

- Although the activity of ^{68}Ga-PSMA-11 in blood can be attributed to body remainder for dose calculations, considering blood as an explicit source region provides a more realistic distribution of ^{68}Ga-PSMA-11 activity and, thus, its contribution to absorbed doses of body organs and tissues. Blood was treated as an explicit source region only in the article by Sandgren et al.

- The comparison of data across conducted studies revealed substantial differences in TIACs for various organs between the work of Demirci et al.and the work of Sandgren et al.. The total number of documented disintegrations differ notably, with Demirci et al. accounting for only nearly half of the disintegrations reported by Sandgren et al. The discrepancies in TIACs for liver, spleen, salivary glands and lacrimal glands were probably caused by the different assumed organ masses used to scale the measured activity concentrations to the activities in whole organs, besides the possible inter-patient variability in measured activity concentrations. The TIACs in urinary bladder contents as well as the total number of disintegrations are highly affected by the assumptions made regarding the bladder voiding. Sandgren et al. assumed conservatively 3.5 hours voiding intervals. Demirci et al. did not report which voiding intervals / voiding times were considered. The lower values reported by Demirci et al. might be explained by shorter voiding intervals assumed than those in Sandgren et al.

Considering the above, the dose coefficients for organ doses and the effective dose obtained by Sandgren et al. are considered more robust and complete than those described by Demirci et al., and are therefore included in the SmPC. Furthermore, since the dose coefficients for 11 organs were not reported in the publication by Sandgren et al., the Applicant has gained access to raw data collected and re-calculated dosimetry in accordance with a methodology closely similar to the one described in the publication. The presented approach for choice of the methodology for recalculation is supported. Sensitivity analyses were conducted to estimate the robustness of the data and absorbed doses per administered activity of the organs presented in the original publication were compared to the re-calculated values. These analyses showed that the maximum difference between the re-calculated values and the original data-set did not differ by more than 10% and that the re-calculated and original effective doses did not differ relevantly either. It is agreed that the differences observed between the re-calculated and original data are not clinically relevant which supports adequacy of the methodology applied for dosimetry calculation for missing organs. The dosimetry table included in the SmPC includes a combination of the original data and the re-calculated dosimetry results for 27 organs including effective dose which is considered appropriate.

Studies in special populations were not submitted. Subgroup analyses to test the possible effects of intrinsic and extrinsic factors on safety were performed on the data in PSMA-617-01 clinical study but did not reveal relevant impact on safety profile of the product. Although, these analyses are not considered adequate to replace a proper study in special populations, different effects in special populations (e.g., race, hepatic impairment) are considered unlikely. Gender effects and studies in children are not relevant given the intended use only in adult males. Also, doses and effects in older and elderly (Typical population) is sufficiently characterised. The risk of increased local radiation exposure and potential impact on renal function (given that kidney is the main elimination pathway) is

regarded negligible due to the micro dosing regimen and short physical half-life of ^{68}Ga. Based on the same arguments, dose adjustment in the patients with renal impairment is considered not necessary. Inter- and intra-patient variability was not assessed, as in the studies, several sources of variability (i.e., disease state, dose, imaging acquisition time, equipment, data collection, data analysis) were present and no proper assessment of true inter-subject variability is possible. This is acceptable.

The Applicant's proposed commercial product was not used in any study. In lieu of bioequivalence studies, quality evidence was referenced (see Quality section) in order to bridge the proposed commercial product to the formulations used in Study PSMA-617-01 as well as to the literature. Notably, composition of the majority of the used formulations in the study is unknown. This, however, is not seen as blocking issue, as the majority of the ^{68}Ga-PSMA-11 products applied in the published studies would be expected to comply with the pharmacopeia monograph (Eur. Ph. 3044) and no interactions between excipients and ^{68}Ga-PSMA-11 would be expected.

Concerns regarding the higher presence of "cold" PSMA-11 in Locametz was raised, because the dose is based on the amount of (bound) Gallium, but the protein content could be higher. This could have implications for its sensitivity compared to the literature. However, this was resolved based on the pre-clinical evidence (Kalidindi et al., 2021), that suggests that no relevant difference in the uptake of ^{68}Ga-PSMA-11 would be expected with up-to 1000 fold increase of "cold" PSMA in the administered solution.

The proposed pH specification is lower than foreseen by the Pharmacopeia monograph "Gallium (68Ga) PSMA-11 Injection" (Eur. Ph. 3044). This may be a safety issue. However, another diagnostic product with similarly low pH has been authorised and in use (pH 3.2 – 3.8; SomaKit TOC by Advanced Accelerator Applications; EMEA/H/C/004140; approved in 2016) with a single injection site reaction – "injection site pain" – reported as an adverse event (AE) related to low pH. Thus, similar safety risks can be expected from ^{68}Ga-Locametz.

It is acknowledged that high osmolality may be relevant for local tolerability of an i.v. formulation. Osmolality of the ^{68}Ga-PSMA-11 formulations applied in VISION and published studies is unknown. The Applicant has introduced an additional mandatory dilution prior to the administration of ^{68}Ga-labeled Locametz (see SmPC section 12) in order to reduce osmolality of the to-be-injected solution. The osmolality of ^{68}Ga-Locametz at the time of injection is now estimated to be roughly within the range of 600 to 800 mOsm/kg (see section Quality aspects), which is below the acknowledged threshold of tolerability of 1000 mOsm/kg for i.v. small volume (≤100 mL) injections (Wang et al., 2015) and acceptable from the safety/tolerability point of view.

Gentisic acid (the single excipient not included in comparator formulations) is applied to stabilize the ^{68}Ga-PSMA-11 complexes. Thus, worsening in the diagnostic performance is not expected. The same excipient is also used in already approved products (e.g. TechneScan and Octreoscan) in quantities that are similar or higher than the amount (i.e. 1 mg) present in the proposed formulation. Thus, no concerns regarding the safety/tolerability, or potential impact on efficacy are being raised in regards to this excipient.

In conclusion, the bridging to the products used in the published studies can be considered established, except for some remaining uncertainty regarding the frequency of injection site reactions, which cannot reliably be estimated currently. However, this is not regarded as a major issue.

In vitro metabolism and interaction studies with transporters and plasma protein binding measurements performed on ^{68}Ga-PSMA-11 indicate that the compound has a low risk for clinically relevant drug-drug interactions.

Pharmacodynamics

PSMA 11 was shown to have high affinity for PSMA, which is usually overexpressed in prostate cancer lesions, in cancerous lymph nodes and other metastases and bone lesions. Administration of ^{68}Ga-labelled PSMA-11 made these tissues detectable with PET visually and by means of semi-quantitative/quantitative measurement methods (e.g., standardised uptake value (SUV)). The most appropriate cut-off value for differentiating physiological uptake in the primary tumour from that in the prostate was found to be an SUVmax of 3.2. The most appropriate cut-off values for differentiating non-pathological uptake in lymph nodes and bones from tumour uptake were found to be SUVmax of 3.2 and 1.9, respectively (Prasad et al.). Increase in tracer uptake in tumour was observed after 3 hours post-injection as compared to 1 h. However, uptake at 1 h was already high enough to suffice for good detectability (Afshar-Oromieh et al.) that supports the proposed imaging time. PD effects are thus sufficiently characterized.

Notably, the tracer also binds to healthy tissues. This may lead to mistakes in image interpretation, especially in pelvic area due to interference with activity in urine bladder. The latter is an acknowledged issue and has been addressed in section 4.4 of the SmPC with recommendation to let patient void prior to PET imaging.

No PD interactions were studied in humans given the low dose administered, single application and lack of potential of interaction. This is in general accepted. However, while no PD interactions in the classical sense are expected, some concomitant medications may have impact on efficacy/diagnostic and technical performance of the product. E.g., Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, have been reported to modulate PSMA expression. Impact of these therapies on diagnostic performance of ^{68}Ga-gozetotide has been reflected in section 4.4 of the SmPC. Furosemide is commonly used as a concomitant medication during injection of ^{68}Ga-PSMA to reduce the extent of signal scatter from the urinary bladder on ^{68}Ga-PSMA-PET images through increased voiding. However, firm evidence sufficient for recommendation of furosemide use is currently lacking, therefore this is not a recommended in the SmPC.

Across the published literature from studies of varying size, aim and design, high sensitivity and specificity were achieved for ^{68}Ga-PSMA-11 PET, supporting the confidence in the performance of ^{68}Ga-PSMA-11 PET to select patients with PSMA-expressing prostate cancer lesions.

No clinical data on secondary pharmacology were submitted. In nonclinical studies addressing the risk for QT interval prolongation, no signs of interference were observed.

No clinical data on secondary pharmacology are available. In nonclinical studies addressing the risk for QT interval prolongation, no signs of interference were observed. This is considered acceptable.

2.6.4. Conclusions on clinical pharmacology

In conclusion, pharmacokinetics of PSMA-11 in humans has not been comprehensively studied and described (e.g., excretion, dose proportionality, PK in the patients with hepatic or renal impairment). However, given the micro-dose applied and single application mode, the presented data package is acceptable. Bridging to other formulations utilized in the published literature and VISION study can be considered established, even though some uncertainty regarding local tolerability remains. The clinical PK and PD data package for ^{68}Ga-PSMA-11 is acceptable. At the chemical concentrations used for diagnostic examinations, ^{68}Ga-PSMA-11 does not have any pharmacodynamic activity. No dose adjustment is required in older patients, in patients with renal impairment or in patients with hepatic impairment. No clinically significant interactions with other medicinal products are expected. Initially,

the applicant selected the study by Demirci et al as a key publication. On request of the CHMP dosimetry data by Sandgren et al. have now been applied in the SmPC.

2.6.5. Clinical efficacy

The Applicant submitted data from two own studies and a large number of published evidence to support efficacy claims. Own studies and two publications were presented as main evidence.

Note: Throughout the clinical dossier the Applicant refers to the PSMA-11 products approved in the USA recently (NDA 212642 and 212643 from UCLA and UCSF). For these products, data cited in the labels or FDA assessment reports cannot be utilized, as, irrespective of the legal basis of the application, assessment reports such as the EPAR for EU marketing authorisations or similar summary reports from competent authorities inside and outside the EU which are made publicly available by competent authorities for reasons of transparency, cannot be considered to meet the requirements of Annex I of Directive 2001/83/EC. Therefore, the respective citations and data have not been considered and included into this report.

2.6.5.1. Dose response study(ies)

No dedicated dose-response study has been submitted.

The recommended dose of ^{68}Ga-PSMA-11 is 1.8-2.2 MBq/kg of body weight (0.049 - 0.059 mCi/kg), with a minimum dose of 111 MBq (3 mCi) up to a maximum dose of 259 MBq (7 mCi). This dose range comprises the proposed radioactivity dose of 1.8 - 2.2 MBq per kg recommended by the Joint EANM and SNMMI procedure guideline for prostate cancer imaging (Fendler et al 2017b) and also in line with the recently approved ^{68}Ga PSMA-11 labels (Gallium Ga 68 PSMA-11 USPI 2020a, Gallium Ga 68 PSMA-11 USPI 2020b). Lower doses than 1.8 MBq/kg were shown to adversely affect image quality and lesion detectability in a simulation experiment (Rauscher et al 2020).

In Study PSMA-617-01, ^{68}Ga-PSMA-11 was planned to be administered intravenously at a dose of 111-185 MBq (3 - 5 mCi) which is within the range of the intended dose of 1.8-2.2 MBq per kg. The actual dose administered to patients in Study PSMA-617-01 ranged from 92.8 MBq (2.5 mCi) to 287.5 MBq (7.8 mCi), with a corresponding body weight adjusted dose range of 0.9-3.7 MBq per kg (median dose: 1.9 MBq/kg). Overall, 149 patients received activity injected-decay corrected dose exceeding 5 mCi (> 185 MBq) with a mean dose of 2.3 MBq/kg in Study PSMA-617-01.

From a safety perspective, dose of 1.8-2.2 MBq/kg results in an effective radiation dose of 2.37-3.87 mSv for an administered activity of 150 MBq (Fendler et al (2017b), Afshar-Oromieh et al (2016), Demirci et al (2018), Green et al (2017), Pfob et al (2016), Sandgren et al (2019)). This level of radioactivity is lower than other PET agents used for prostate cancer imaging and well within the effective dose from a diagnostic CT. For a 7 mCi (259 MBq) dose, at the maximum end of the proposed commercial dose range, the effective dose would be 6.68 mSv. This radiation exposure is in range with other standard of care radio-diagnostic procedures (e.g. a diagnostic CT scan would lead to approximately 15-20 mSv) (McCollough et al 2015, Martí-Climent 2017, Akin et al 2017).

Maximum volume of up to 10 ml of ^{68}Ga-Locametz is recommended to be administered.

Amount of the PSMA-11

In terms of mass dose, one dose of ^{68}Ga PSMA 11 prepared from PSMA-11 Sterile Cold kit contains not more than 25 µg total mass.

Imaging time

Based on the use of ^{68}Ga-PSMA-11 in Study PSMA-617-01, as well as published clinical experience and the Joint EANM and SNMMI procedure guideline for prostate cancer imaging (Fendler et al 2017), the recommended imaging time is at 50-100 minutes after the i.v. administration of ^{68}Ga-PSMA-11.

Afshar-Oromieh et al (2013) showed that metastases and recurrent prostate cancer were visualized with adequate contrast at 1 h p.i. of the ^{68}Ga PSMA 11, contributing to a good detection rate of lesions suspicious for cancer even at low PSA levels. This was supported by the observation that all of the 65 lesions suspicious for cancer were clearly seen in 1 h p.i. images.

2.6.5.2. Evidence of efficacy – primary staging in patients with confirmed PCa

2.6.5.2.1. Studies evaluating diagnostic performance – primary staging

Studies submitted to support diagnostic performance in primary staging of PCa are summarised in the table below. More relevant/robust studies are briefly described separately.

Table 4: Evidence of efficacy from published literature for the identification of PSMA-positive lesions – Primary staging

Reference Country	No. of Pats Enroll/ analys	Standard of Truth	PET scan Reads (Visual assessment)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	Detect Rate (95% CI)
Biopsy-proven prostate cancer before curative-intent therapy (primary staging)									
Woythal et al (2018) Germany	31	Histology	Two experienced readers	97%	90%	NA	NA	NA	NA
Basha et al (2019) Egypt	173 / 173	Histopathology	Five independent blinded readers. Consensus for disagreements	96% (91.84%-98.36%)	No true-negative patients	NA	NA	NA	NA
Yaxley et al (2019)	208/ 208	Histopathology	Multiple experienced readers	Patient based: 38.2% (25.4-52.3%) Per node:24.4% (18.2-31.5%)	Patient based: 93.5% (88.3-96.8%) Per node: 99.5% (99.2-99.7%)	Patient based: 67.7% (48.6-83.3%) Per node: 75% (61.6-85.6%)	Patient based: 80.8% (74.2-86.3%) Per node:95.5% (94.7-96.2%)	62%	NA
Hofman et al (2020) Australia	302/ 148	Comp Truth Standard (CTS) including histopath, imaging, and biochemistry at 6-month	Several readers (number NA), some involved in the trial. Results of first-line imaging available when reporting second-line imaging	85% (74-96%)	98% (95-100%)	NA	NA	92% (88-95%)	NA
van Kalmthout et al (2020) Netherlands	103 / 97	Histopathology for lymph node metastases	Two independent blinded readers. Third reviewer consensus if discrepancies	Patient based: 41.5% (26.7-57.8%) Template based: 35.1 (23.2-48.9)	Patient based: 90.9% (79.3-96.6%) Template based: 96.4 (93.5-98.1)	Patient based: 77.3% (54.2-91.3%) Template based: 64.5 (45.4-80.2)	Patient based: 67.6% (55.6-77.7%) Template based: 89.0 (85.0-92.0)	NA	NA

Reference Country	No. of Pats Enroll/ analys	Standard of Truth	PET scan Reads (Visual assessment)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	Detect Rate (95% CI)
Maurer et al (2016) Germany	130	Histology	One blinded reader	Patient based: 65.9% (49.4-79.9%) Template based: 73.5% (62.1-82.5%)	Patient based: 98.9% (93.9-100%) Template based: 99.2% (97.8-99.7%)	Patient based: 96.4% Template based: 94.5%	Patient based: 86.3% Template based: 95.2%	Patient based: 88.5% (81.7-93.4%) Template based: 95.1% (92.6-96.8%)	Patient based: 65.9% Template based: 73.5%
Kopp et al (2020) Germany	90	Histopathology	One blinded reader	Patient-based: 43.8% per-pelvic side: 42.9% Region-based: 47.6%	Patient based: 96.0% per-pelvic side: 95.6% Region-based: 98.9%	Patient based: 70.0% per-pelvic side: 56.3% Region-based: 66.7%	Patient based: 88.8% per-pelvic side: 92.7% Region-based: 97.5%	NA	NA
Lengana et al (2018) South Africa and Belgium	113 / 113	CTS including CT, MRI, skeletal survey, clinical follow-up, and histologic correlation	Two experienced, blinded readers. Consensus for disagreement.	96.2%	100.0%	100.0%	98.9%	99.1%	98.2%
Hope et al., 2021	764/277	Histopathology for lymph node metastases	3 Blinded independent central reads (majority consensus read 2:1)	40% (34-46%)	95% (92-97%)	75% (70-80%)	81% (76-85%)	NA	NA

Hofman et al (2020) conducted a prospective, multicenter, two-arm, randomized, Phase 3 study in men with high-risk, biopsy-proven PCa, who were being considered for radical prostatectomy or radiotherapy with curative intent. The trial aimed to investigate whether PSMA PET-CT had improved accuracy when compared with the combination of CT and bone scan. The diagnostic utility of PSMA PET-CT as a replacement for conventional imaging was explored.

Cross-over imaging was done within 14 days of the first-line imaging. Results of first-line imaging were available when reporting second-line imaging. Imaging was interpreted by experienced radiologists and nuclear medicine specialists, some of whom were further involved with the trial. At 6 months repeat imaging as per randomised group was done.

The primary outcome of the trial was accuracy (assessed by the area under the curve (AUC) of the receiver operating characteristic curve) of first-line imaging for identifying either pelvic nodal or distant metastatic disease. The AUC was calculated as the mean of the estimated sensitivity and specificity.

The reference standard was determined by each site's principal investigator at 6 months using a predefined composite criteria. Cases were considered positive if one of the hard or at least three soft criteria were met.

Table 5: Hard and soft criteria for definition of SOT/composite SOT

Hard criteria 1. Histopathology demonstrating prostate adenocarcinoma (pathology report and/or clinical notes) 2. Change of bone lesion to sclerotic/blastic on follow-up imaging assessment (results of imaging reports and/or clinical notes)*
Soft criteria 3. Typical appearance of multi-focal metastatic disease (results of imaging reports) 4. Appearance of a metastatic lesion on an imaging modality other than the one performed as the index scan (results of imaging reports and/or clinical notes) 5. Increase in the number or size of bone lesion(s)* or soft tissue lesion(s) from one imaging exam to the next, over time following the index scan (results of imaging reports and/or clinical notes) 6. Decrease in the number or size of bone lesion(s)* or soft tissue lesion(s) following disease-appropriate treatment from one imaging exam to the next, over time following the index scan (results of imaging reports and/or clinical notes) 7. Presence of a lesion on an initial imaging examination with associated clinical symptoms suggesting malignancy (results of imaging reports and/or clinical notes) 8. Patient received localised treatment for metastasis (e.g. radiotherapy) (clinical notes) 9. Increasing alkaline phosphatase (ALP) or prostate specific antigen (PSA) in keeping with clinical scenario of progression, or decreasing levels in response to treatment (laboratory results showing increase/decrease and/or clinical notes)* 10. Increasing prostate specific antigen (PSA) in keeping with clinical scenario of progression, decreasing levels in response to treatment, or PSA >0.2 ng/ml at least three weeks following prostatectomy. (laboratory results showing increase/decrease and/or clinical notes)** 11. Unequivocal persistence of positive finding present on the baseline scan on repeat imaging at 6 months, in setting of PSA >0.2 ng/ml at least three weeks following prostatectomy (results of imaging reports, laboratory results and/or clinical notes)**

*for distant metastatic disease only; ** for nodal disease only | defined by local principal investigator in conjunction with local multi-disciplinary team using all available information until 6 month (± 30 days) follow-up

The reference standard was defined separately for pelvic nodal and distant metastases. All available imaging and follow-up including second-line imaging, if done, was used to define hard and soft criteria.

Intended management and change in patient management was collected prospectively at baseline, after first-line and second-line imaging. Management decisions were considered in the setting of support from multi-disciplinary genitourinary oncology teams in participating academic centres. Management change was defined by a change in treatment intent (e.g., curative to palliative), addition

or removal of a treatment modality, or change in surgery or radiotherapy technique. Change was classified as high (change in management intent or modality), medium (change in modality delivery), low (management plan was not altered), or potential effect ignored (management plan not altered despite findings showing distant metastatic disease).

PSMA PET-CT images were reviewed also by a central imaging laboratory of expert readers (blinding not reported).

Statistics: a sample size of 300 patients (150 per group) was calculated to achieve a power of 0·85 using the following pragmatic assumptions: (1) conventional imaging has a true underlying AUC of 0·65, consisting of a sensitivity of 0·65 and a specificity of 0·65; (2) PSMA PET-CT has a true underlying AUC of 0·9, consisting of a sensitivity of 0·9 and a specificity of 0·9; (3) the proportion of patients with pelvic nodal or distant metastatic disease is 25%; (4) a margin of 10% improvement (absolute) in AUC is required to declare PSMA PET-CT superior; (5) a two sided type I error of 10%; and (6) allow for a 10% patient dropout. The initial sample of 200 patients was based on an estimated proportion of cases of 40%, that was later revised to 25% (without reviewing study data).

For the primary endpoint, all participants with first-line imaging and reference standard were included in the analysis. Lesions rated as equivocal were considered negative for metastatic disease. The primary analysis was a patient-level analysis. The p-value for the null hypothesis that the AUC for PSMA PET-CT is 10% greater (absolutely) than the AUC in the conventional imaging group.

The analyses of the primary objective were repeated for nodal and distant metastatic groups and sensitivity analysis was done in which equivocal lesions were considered positive for metastases.

For secondary outcomes, the proportion of patients with management effect and equivocal findings were compared using Fisher's exact test. Radiation exposure was compared using Student's unpaired t-test. Reporter agreement between local and central readers were assessed using Cohen's weighted κ. To assess the incremental accuracy of second-line imaging, the proportion of patients who were upstaged by identification of nodal or distant metastases was calculated; the number of patients who were accurately or inaccurately upstaged using the 6-month reference standard was also calculated.

Results: A total of 302 men (median age, IQR: 69.0 years, 63.0-73.5) were recruited. 293 (98%) men had tumour of ISUP grade group 3 or more, 65 (22%) with PSA concentration of 20 ng/mL or more (half with less than 10 ng/mL), and 82 (27%) men with clinical stage T3–4. Data from a total of 150 patients from the conventional imaging group and 145 patients from the PSMA PET-CT group were used in the primary endpoint analysis.

Mean (SD) dose of 162.8 (39.6) for first-line imaging and mean (SD) time from injection to start of scan of 62.6 (19.0) min was reported. Patient populations in the two arms were roughly similar.

Compared to conventional imaging with CT and bone scan, PSMA PET-CT demonstrated greater accuracy (92%; 95% CI: 88–95% vs. 65%; 95% CI: 60–69%; $p < 0.0001$), higher sensitivity (85%; 95% CI: 74–96% vs. 38%; 95% CI: 24–52%), and higher specificity (98%; 95% CI: 95–100% vs. 91%; 95% CI: 85–97%) at the patient-level. There were also fewer equivocal results (7%; 95% CI: 4–13% vs. 23%; 95% CI: 17–31%, $p < 0.001$) and lower radiation exposure (8.4 mSv; 95% CI: 8.1–8.7 vs.19.2 mSv; 95% CI: 18.2–20.3). A sensitivity analysis in which lesions that were rated as equivocal were considered positive instead of negative for metastatic disease, as well as subgroup analyses on patients with pelvic nodal and distant metastatic disease, showed consistently superior results for PSMA PET-CT with respect to accuracy. Level of agreement of two central readers with local readers was high with PSMA PET-CT for nodal (Cohen's weighted $\kappa = 0.87$, 95% CI: 0.81–0.94) and distant metastatic disease (0.88, 95% CI: 0.84–0.92).

Figure 5: Accuracy, sensitivity, and specificity of conventional imaging compared with PSMA PET-CT

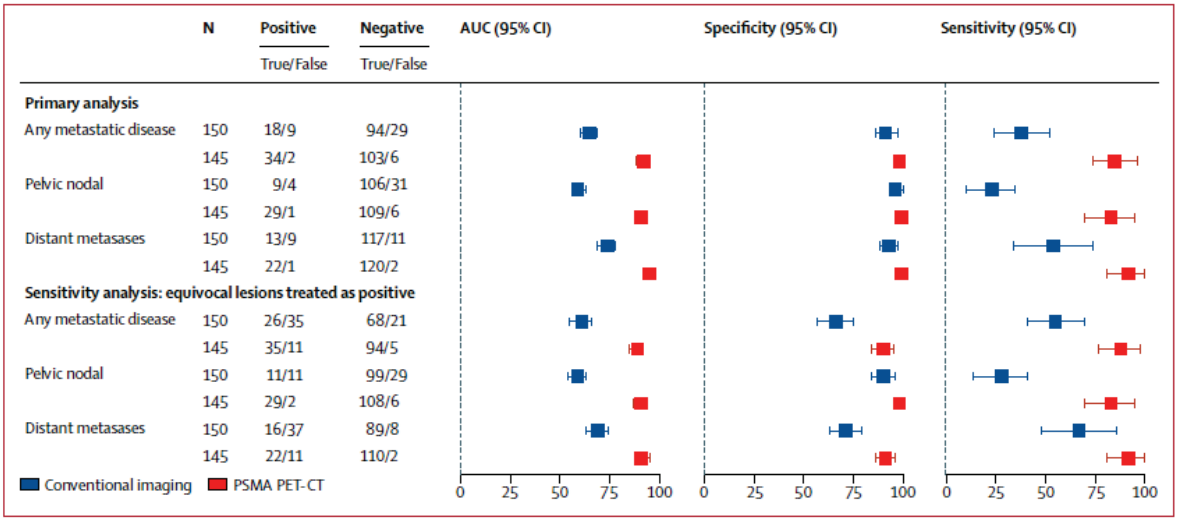
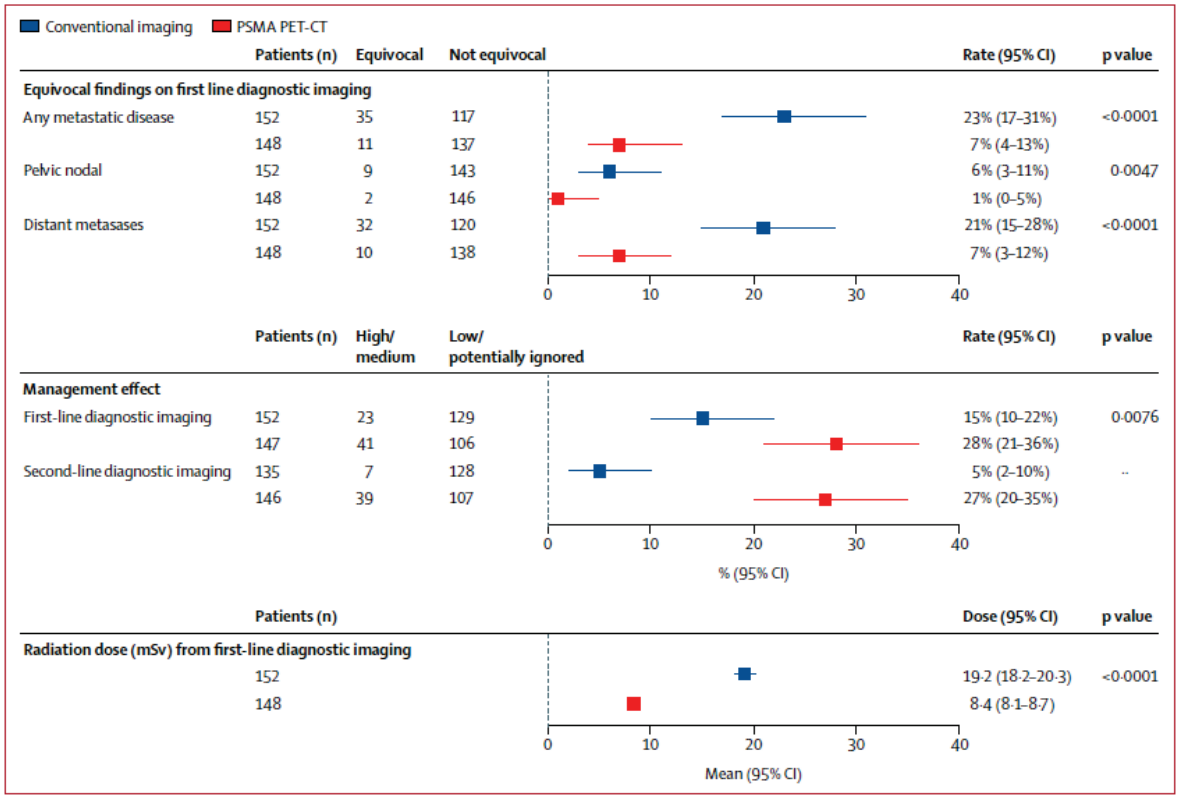


Figure 6: Equivocal findings, management effect, and radiation exposure of conventional imaging compared with PSMA PET-CT



Management change was more frequently reported after PSMA PET-CT compared to conventional imaging, for both first-line PSMA PET-CT (28%; 95% CI: 21–36% vs. 15%; 95% CI: 10–22%, p = 0.008), and second-line PSMA PET-CT (27%; 95% CI: 20–35 vs. 5%; 95% CI: 2–10). Compared with the reference standard, changes in staging were correct in 26 patients (18%; 95% CI: 12–25%) for PSMA PET-CT vs. 3 patients (2%; 95% CI: 0–6%) for conventional imaging. Transition from curative

to palliative intent treatment was identified in 14% of patients and change in treatment approach was found in another 14%.

van Kalmthout et al (2020) conducted a prospective, multicenter study to evaluate the diagnostic accuracy of ^{68}Ga-PSMA PET/CT in detection of lymph node metastasis during primary staging before external pelvic lymph node dissection (ePLND) in newly diagnosed PC patients. A total of 103 intermediate (n=11) to high risk (n=92) PC patients (median age, range: 70 years, 53-82) were included. All patients had biopsy-proven PC, a negative bone scan, and were at > 10% risk for lymph node metastasis, according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria. An intravenous dose of 1.5 MBq/kg of ^{68}Ga-PSMA-11 was administered; PET scans were acquired 60 minutes after injection. ^{68}Ga-PSMA PET/CT scans were first assessed by nuclear medicine physicians, whose readings was used for the assessment of impact in patient management and then assessed in a second round of review by 2 independent blinded reviewers who rated suspicious pathology findings in the prostate region, regional and nonregional lymph nodes, and osseous and visceral lesions according to a 5-point scale. A third independent reviewer was used in case of discrepancies. The sensitivity, specificity, PPV, and NPV of ^{68}Ga-PSMA PET/CT were calculated per patient and per resection template. Histopathology after ePLND was used as the reference standard. Change in management was recorded.

Out of 97 patients that underwent ePLND, 41 (42.3%) had histologically identified 85 lymph node metastases, with positive PET scans for 17 patients. Patient-level sensitivity, specificity, PPV, and NPV of ^{68}Ga-PSMA PET/CT were 41.5% (95% CI: 26.7-57.8), 90.9% (95% CI: 79.3-96.6), 77.3% (95% CI: 54.2-91.3), and 67.6% (95% CI: 55.6-77.7), respectively. Template-based sensitivity, specificity, PPV, and NPV ^{68}Ga-PSMA PET/CT were 35.1% (95% CI: 23.2-48.9), 96.4% (95% CI: 93.5-98.1), 64.5% (95% CI: 45.4-80.2), and 89.0% (95% CI: 85.0-92.0), respectively.

Median diameter of the PET-avid regional lymph node metastasis was 7.0 mm (range 0.3 to 35.0). Of the 41 lymph node metastases that were missed in ^{68}Ga-PSMA PET/CT readings, the median metastatic deposit was 3.0 mm (range 0.5 to 35.0). The difference between the median sizes of detected vs. missed lymph node metastases was significant (7.0 vs. 3.0 mm, $p = 0.04$).

Agreement was moderate ($\kappa = 0.58$) among the nuclear medicine physicians examining the images. Interreader agreement was substantial ($\kappa = 0.67$) for the 2 independent blinded readers in the second scan review. A third reviewer reached consensus in 45 discordant imaging reports.

Based on PET findings and subsequent tumor board discussions on these findings, a treatment change occurred in 13 patients (12.6%): the ePLND template was extended in 6 cases and canceled in another 6 cases; and 5.8% of patients avoided having to undergo an unnecessary invasive operation due to distant metastasis.

Yaxley et al (2019) conducted a retrospective study in 208 patients (median age, range: 68 years, 44-80) with intermediate (n=85) and high risk (n=123) PC to assess the ability of ^{68}Ga-PSMA-11 PET/CT in predicting pelvic lymph node metastasis before pelvic lymph node dissection (PLND) and radical prostatectomy. The primary objective of the study evaluated the sensitivity, specificity, PPV, and NPV of ^{68}Ga-PSMA-11 PET/CT imaging on a per patient and per nodal basis. Histopathology was used as the standard of truth by which to compare the imaging results for both primary tumor and lymph node metastasis; all pathology findings were reviewed by 3 experienced uropathologists. The average injected dose of ^{68}Ga-PSMA-11 was 200 MBq, with a minimum uptake time of 45-60 minutes following injection. PET scans were read by experienced nuclear physician radiologists. Primary staging of patients, using ^{68}Ga-PSMA-11 PET/CT, was implemented prior to PLND and radical prostatectomy, and pre-treatment values for PSA (median, range: 7.6 ug/l, 1.5-51), Gleason score 4 + 5, and ISUP score (median: 5) were collected.

Primary prostate tumors were detected in 95.2% of the patients, with a standardized uptake value (SUV) of ≥ 3. The median long axis diameter of malignant nodes identified on histology was 4.8 mm (range 0.2 to 40). The median long axis diameter of malignant nodes identified as positive by PSMA in concordance with histology was 6.8 mm (range 0.2 to 40). Only 14.6% of histologically confirmed positive lymph nodes with a long axis < 5 mm in diameter were identified by 68Ga-PSMA PET/CT prior to PLND. On a per patient basis, 177 patients had negative findings with 68Ga-PSMA-11 PET/CT, while 34 of these patients showed histological evidence of lymph node metastasis, resulting in an NPV of 80.8% (95% CI 74.2-86.3). Twenty-one patients were histologically confirmed as positive for lymph node metastasis (out of 31 patients with positive 68Ga-PSMA-11 PET/CT imaging), resulting in a PPV of 67.7% (95% CI 48.6-83.3). Twenty-one out the 55 patients with histologically-confirmed metastasis were positively identified with 68Ga-PSMA-11 PET/CT for a patient-level sensitivity of 38.2% (95% CI: 25.4-52.3). Out of 153 patients with histologically confirmed negative lymph nodes, 143 were negative with 68Ga-PSMA-11 PET/CT for a patient-level specificity of 93.5% (95% CI: 88.3-96.8). Per patient sensitivity, specificity, PPV, and NPV were 54.5% (95% CI: 23.4-83.3%), 95.9% (95% CI: 88.6-99.2%), 66.7% (95% CI: 29.9-92.5%), and 93.4% (95% CI: 85.3-97.8%), respectively, for intermediate risk PC (ISUP 2-3); these values were 34.1% (95% CI: 20.5-49.9%), 91.1% (82.6-96.4%), 68.2% (95% CI: 45.1-86.1%), and 71.3% (95% CI: 61.4-79.9%), respectively, for high risk PC (ISUP 4-5).

Per nodal analysis of a total of 2,960 dissected lymph nodes revealed a sensitivity of 24.4% (95% CI: 18.2-31.5%; 42 lymph nodes positively identified by 68Ga-PSMA-11 PET/CT out of 172 histologically confirmed lymph nodes) and specificity of 99.5% (95% CI: 99.2-99.7%; 2764 negatively identified lymph nodes by 68Ga-PSMA-11 PET/CT out of 2788 histologically confirmed negative lymph nodes). PPV per node was 75% (95% CI: 61.6-85.6%) and NPV per node was 95.5% (95% CI: 94.7-96.2%).

Hope et al. (2021) conducted a prospective, multicenter, open-label single-arm phase 3 trial in men with intermediate or high-risk biopsy-proved PC. The purpose of the study was to assess the accuracy of [^{68}Ga]Ga-PSMA-11 PET imaging for the detection of pelvic nodal metastases compared with histopathology at time of radical prostatectomy and pelvic lymph node dissection. The primary objective analyzed the sensitivity and specificity for the detection pelvic lymph nodes compared with histopathology on a per-patient basis using nodal region correlation.

A total of 764 men (median age, IQR: 69 years, 63-73) underwent [^{68}Ga]Ga-PSMA-11 PET imaging for primary staging, and 277 of 764 (36%) subsequently underwent prostatectomy with lymph node dissection (efficacy analysis cohort). Based on pathology reports, 75 of 277 patients (27%) had pelvic nodal metastasis.

Each [^{68}Ga]Ga-PSMA-11 PET study was read locally by board certified nuclear medicine physicians with access to all medical information to generate clinical reports. The [^{68}Ga]Ga-PSMA-11 PET images and report were sent to the referring physician, and treatment decisions were allowed to be based on the PET results. Each imaging study of the primary efficacy population (patients who underwent radical prostatectomy) was read by 3 blinded independent central readers, not involved in study design and data acquisition. In total, 6 blinded readers were used from outside institutions and were required to complete a training on 30 cases from a previously published data set. For analysis, a centralized per-region majority rule was generated by the local investigators. In patients who underwent prostatectomy after imaging, the surgical pathology report was obtained. The surgical approach was not standardized, and no resection template was required. The investigators coded the histopathology reference standard as negative or positive for pelvic lymph node metastasis.

Of the 277 in the surgical cohort, median age was 67 (IQR 61-71). 49 (18%) men had intermediate risk PC and 225 (81%) had high-risk PC, with a median PSA of 11.1 ng/mL (IQR 6.5-18.0) and 220/277 (79.4%) had an ISUP grade group ≥3. A total of 75 of 277 patients (27%) had regional pelvic

node metastasis found on pathology (pN1). The median (IQR) size of the largest positive lymph node on pathology per patient was 6 (3-10) mm.

On a per-patient level, the sensitivity, specificity, PPV, and NPV of [^{68}Ga]Ga-PSMA-11 PET based on the majority reads were 0.40 (95% CI, 0.34-0.46), 0.95 (95% CI, 0.92-0.97), 0.75 (95% CI, 0.70-0.80), and 0.81 (95% CI, 0.76-0.85).

In a post hoc retrospective analysis, they determined if PSA level, Gleason score, D'Amico risk, and node size were associated with the sensitivity, specificity, PPV, and NPV of [^{68}Ga]Ga-PSMA-11 PET. Larger pelvic lymph node metastasis size (>10 mm) was associated with higher sensitivity of [^{68}Ga]Ga-PSMA-11 PET (0.59 (95% CI 0.41, 0.75) for the detection of pelvic nodal metastases. True-positive and FN pelvic lymph node metastasis measured an average of 1.1 cm and 0.6 cm, respectively (p = .01). There was insufficient evidence to conclude that Gleason score, PSA level (categorized) and D'Amico risk were associated with sensitivity.

The study did not meet the predefined threshold sensitivity of 0.65.

2.6.5.2.2. Impact on patient management – primary staging of PCa

A summary of the data showing the impact of the ^{68}Ga-PSMA-11 PET on PC management is provided in table below.

In primary staging, 21% to 67% of patients were re-staged due to findings from ^{68}Ga-PSMA-11 PET/CT (Hruby et al 2018, Roach et al 2018, Basha et al 2019, Sonni et al 2020). In the four studies focused on primary staging of patients, the intended change in patient management ranged from 21% to 28% (Roach et al 2018, Hofman et al 2020) and implemented change in patient management in 12.6% to 43% of patients (Sonni et al 2020, van Kalmthout et al 2020).

Table 6: Clinical impact in PC patient management from published literature (Primary staging)

Reference Country	No. of Patients Enrolled / Analysed	Method of assessment	Pre-PET stage changed after ^{68}Ga-PSMA-11 PET/CT	Intended change in therapy	Implemented change in therapy
Primary Staging					
Hofman et al (2020) Australia	150 / 147	Questionnaires	NA*	41/147 (28%)	NA*
Roach et al (2018) Australia	431 / 108	Questionnaires	Disease state: More extensive: 22/108 (20%) Less extensive: 1/108 (1%) Unchanged: 81/108 (75%) Unsure/equivocal: 4/108 (4%)	23/108 (21%)	NA
van Kalmthout et al (2020) Netherlands	103 / 103	Tumor board	NA	NA	13/103 (12.6%)
Sonni et al (2020) USA	197 / 30	Questionnaires	20/30 (67%)	NA	12/28 (43%)

Reference Country	No. of Patients Enrolled / Analysed	Method of assessment	Pre-PET stage changed after ^{68}Ga-PSMA-11 PET/CT	Intended change in therapy	Implemented change in therapy
Basha et al (2019) Egypt	173 / 112	NA	32/112 (28.6%) Upstage: 20/112 (17.9%) Downstage: 12/112 (10.7%)	NA	NA
Hruby et al (2018) Australia	109 / 109	Conventional imaging	26/109 (23.9%) Upstage: 23/109 (21.1%) Downstage: 3/109 (2.8%)	NA	NA
*based on first-line imaging					

2.6.5.3. Evidence of efficacy – BCR

2.6.5.3.1. Studies evaluating diagnostic performance – BCR

Studies submitted to support diagnostic performance in biochemical recurrence of PCa (BCR) are summarised in the table below. More relevant/robust studies are briefly described separately.

Table 7: Evidence of efficacy from published literature for the identification of PSMA-positive lesions - BCR

Reference Country	No. of Patients Enrolled/ Analysed	Standard of Truth	PET scan Reads (Visual assessment)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	Detection Rate (95% CI)
BCR of prostate cancer after definitive therapy with prostatectomy or radiotherapy									
Fendler et al (2019) USA	635 / 79-84	Histopathology	Cases were divided randomly between 9 blinded readers, to obtain 3 independent reads per patient	Patient based: 92% (84-96%) Region based: 90% (82-95%)	NA	Patient based: 84% (75-90%) Region-based: 84% (76-91%)	NA	NA	75%
	635 / 217-249	CTS including histopathology, imaging, and PSA at 6-month		NA NA	NA	Patient-based: 92% (88-95%) Region-based: 92% (88-95%)	NA	NA	
Ceci et al (2019) Italy	332 / 105	Histopathology (n=10) / Imaging or clinical follow-up	Two independent readers. Third reviewer for final output if discrepancies	NA	NA	96.2% (95.6%-96.7%	NA	NA	53.6% (48.1%-59.1%)

Reference Country	No. of Patients Enrolled/ Analysed	Standard of Truth	PET scan Reads (Visual assessment)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	Detection Rate (95% CI)
Deandris et al (2020) Italy	223 / 65	Pathology (n=17); Imaging+clinical follow-up (n=48)	Three independent readers unblinded to clinical data. Majority rule in case of reader disagreement (2:1)	NA	NA	NA	NA	NA	39.9% (33.5-46.7%)
Hamed et al (2019) Egypt	188 / 188	Histopathology (n=151)/Clinical and Imaging (n=37)	Two central independent blinded readers. Consensus for discrepancies	98.8% (95.74-99.85%)	100% (83.89-100.0%)	100% (97.79-100.0%)	91.3% (71.96-98.93%)	98.8%	87.8%
Lawhn-Heath et al (2019) USA	150 (72 in analysis reader average)	Histopathology (n=43)/Clinical and Imaging (n=29)	Two independent blinded readers	89.1%	31.2%	90.6%	24.7%	NA	80.6%

Fendler et al (2019)

(Note: part of the data in this publication formed part of the UCLA data contribution to the FDA submitted application that was approved in December 2020 and also overlaps with Fendler et al (2020)).

This was a prospective, multicenter, single-arm study, designed to assess the accuracy of ^{68}Ga-PSMA-11 PET imaging in localizing recurrent PC. Patients with biopsy-confirmed prostate cancer after radical surgical treatment and/or radiation therapy (RT) with increased levels of PSA (0.2 ng/mL or greater measured during 6-13 weeks post-surgery, or Nadir equal or greater than 2 ng/mL after RT).

The key endpoint used to evaluate accuracy was the PPV of ^{68}Ga-PSMA-11 PET on a per-patient and per region basis. Lesions were validated by histopathologic analysis (primary endpoint) and a composite reference standard (secondary endpoint). A combination of histopathologic analysis, imaging (including CT, MRI, and/or bone scan), and PSA follow-up after local/focal therapy was used (in descending priority) as the composite reference standard. Other secondary endpoints included sensitivity (per-patient and per-region), detection rate (stratified by PSA levels and PSA doubling time), inter-reader agreement, and safety. Patients received an average of 5.1 (SD: 1.1) mCi of ^{68}Ga-PSMA-11 and 20 mg of furosemide at a mean (SD) 64 (13) min before the scan. Furosemide was given to 588 (93%) of 635 patients to minimize pelvic scatter artifacts.

Image interpretation: 9 independent readers reviewed the ^{68}Ga-PSMA-11 scans, with each patient scan read by 3 partially blinded readers. Data sets for reader interpretation included whole-body PET (attenuation corrected and non-corrected), whole-body post-contrast CT, or whole-body post-gadolinium T1 and pelvic T2 MRI. Readers were provided recent PSA level and type of primary therapy (prostatectomy vs radiation therapy), but were blind to all other information. Presence of prostate cancer (positive vs negative) was recorded for 4 regions (prostate bed, pelvic nodes, extra-pelvic non-bone, bone) and a total of 21 sub-regions. Pelvic lymph nodes (LN) were grouped in 7 sub-regions: R/L obturator, R/L external iliac, R/L internal iliac and other. Majority vote was used in cases of reader disagreement.

Validation of 68Ga-PSMA-11 PET findings was based on histology or follow-up (3-12 months):

- PSMA-avid LNs (3-12 months follow-up): True positives (TP) were defined as the PSMA-avid LNs, which decrease in more than 30% in size on CT or MRI (treated patients), or increase by more than 20% in short axis diameter (min 3 mm change), OR if, in patients with solitary LN, PSA decreased by more than 50% after targeted treatment (i.e., external beam radiation) and LN do not change in size. False positive (FP) LNs were defined as LNs with >30% decrease in size on follow-up imaging without treatment at this site, or those not meeting the above criteria for TP or FP.
- PET-positive Visceral lesions (3-12 months follow-up): as TP were regarded the lesions with >30% decrease in size on targeted therapy, or >20% increase in largest diameter. FP were the lesions with >30% decrease in size without systemic or targeted therapy at the site, or those not meeting the other TP or FP criteria.
- Bone lesions: TP were defined as those with corresponding sclerotic lesion on the CT portion of 68Ga-PSMA-11 PET in the same location, or focal uptake observed on baseline bone scan, or on MRI, or if follow-up (12 months) CT, MRI, or bone scan show changes suggestive of bone lesion. FP was defined as all PET-positive bone lesions not meeting the criteria of TP.
- Prostate bed lesions: TP was defined in the similar way as TP for visceral lesions (change in size) and LNs (change in PSA) but based on 12 months follow-up. FP was defined similar to those of LN and visceral lesions.

No true negative (TN) cases were defined.

Statistics: The null hypothesis was that the true PPV is 0.50, whereas the alternative hypothesis was that the true PPV is at least 0.70.

Enrollment was completed when 114 patients had biopsy and/or surgery follow-up, fulfilling protocol requirements for analysis of the per-patient–based primary endpoint (≥107 patients with biopsy and/or surgery follow-up, 90% power, 1-sided .01 significance level).

Secondary endpoints were per-patient and per-region PPV confirmed by composite validation, per-patient and per region sensitivity (SE) confirmed by histopathologic validation, per-patient detection rate stratified by PSA and PSA doubling time, inter-reader agreement, and safety. Detection rate was defined as proportion of patients with PSMA PET positive results, independent of the reference standard. Inter-reader agreement was determined by Fleiss' κ and interpreted by criteria of Landis and Koch.

Results: A total of 635 patients (median age, range: 69 years, 44-95) were included in the study who had biochemically recurrent PC after prostatectomy (n = 262, 41%), radiation therapy (n = 169, 27%), or both (n = 204, 32%). Due to exclusion of 46 patients (as a result of location mismatch between PET and follow-up, or absence of PC on PET and histological examination), the efficacy analysis consisted of 223 patients with composite validation and 93 with histopathologic validation.

Table 8*: *Baseline characteristics of the patients included (Fendler et al (2019))

	No. (%)		
		Efficacy Cohort	
Characteristic	All Patients (N = 635)	Composite (N = 223)	Histopathologic (N = 93)
Age, median (range), y	69 (44-95)	70 (49-88)	71 (49-88)
Initial therapy			
Prostatectomy only	262 (41)	60 (27)	22 (24)
Radiation therapy only	169 (27)	80 (36)	50 (54)
Prostatectomy and salvage radiation therapy	204 (32)	83 (37)	21 (23)
Other prior therapy			
Local salvage therapy	85 (13)	35 (16)	9 (10)
Androgen deprivation	244 (38)	110 (49)	31 (33)
Abiraterone/enzalutamide	15 (2)	13 (6)	1 (1)
Chemotherapy	14 (2)	12 (5)	1 (1)
Bone-targeted treatment	6 (1)	6 (3)	0 (0)
Other	32 (5)	19 (9)	3 (3)
Time from initial therapy to PET, y			
Median (range)	5 (0-33)	6 (0-29)	6 (0-29)
<5	309 (49)	97 (43)	34 (37)
≥5	307 (48)	118 (53)	57 (61)
Not available	19 (3)	8 (4)	2 (2)
Gleason score			
<8	378 (60)	128 (57)	68 (73)
≥8	202 (32)	82 (37)	21 (23)
Not available	55 (9)	13 (6)	4 (4)
PSA, median (range), ng/mL[a]	2.1 (0.1-1154.0)	3.5 (0.1-1154.0)	3.9 (0.1-70.6)
PSA doubling time, median (range), mo[b]	6 (0->120)	6 (1->120)	10 (1-73)

On a per-patient basis, the PPV was 0.84 (95% CI: 0.75-0.90) by histopathologic validation (n = 87) and 0.92 (95% CI: 0.88-0.95) by the composite reference standard (n = 217). On a per-region basis, the PPV was 0.84 (95% CI, 0.76-0.91) by histopathologic validation (n = 90) and 0.92 (95% CI, 0.88-

0.95) by the composite reference standard (n = 249). Sensitivity by histopathologic validation was 0.92 (95% CI, 0.84-0.96) on a per-patient basis, and 0.90 (95% CI, 0.82-0.95) on a per-region basis.

Table 9: Diagnostic performance of 68Ga-PSMA-11 PET (Fendler et al (2019))

Validation Group	Total Regions/ Patients, No.	No. (%) Confirmed	No. (%) Ruled Out	PPV or SE (95%CI)
Positive Predictive Value				
Composite validation				
PET positive (per-patient)	217	200 (92)	17 (8)	0.92 (0.88-0.95)
PET positive (per-region)	249	229 (92)	20 (8)	0.92 (0.88-0.95)
Histopathologic validation				
PET positive (per-patient)	87	73 (84)	14 (16)	0.84 (0.75-0.90)
PET positive (per-region)	90	76 (84)	14 (16)	0.84 (0.76-0.91)
Sensitivity				
Histopathologic findings				
Confirmed (per-patient)	79	73 (92)[a]	6 (8)[b]	0.92 (0.84-0.96)
Confirmed (per-region)	84	76 (90)[a]	8 (10)[b]	0.90 (0.82-0.95)

Abbreviations: PET, positron emission tomography; PPV, positive predictive value; SE, sensitivity.
a PET positive.
b PET negative.

Overall, PET false-positive lesions were reported in few patients, most in the prostate or prostate bed (11 of 17 patients [65%]).

Overall, the detection rate of ^{68}Ga-PSMA-11 PET (PSMA PET positive results, independent of the reference standard) was 75%. Detection rates significantly increased with PSA: 38% for < 0.5 ng/mL (n = 136), 57% for 0.5 to < 1.0 ng/mL (n = 79), 84% for 1.0 to < 2.0 ng/mL (n = 89), 86% for 2.0 to < 5.0 ng/mL (n = 158), and 97% for ≥ 5.0 ng/mL (n = 173), p < 0.001. No significant association was observed between detection rate and PSA doubling time or PSA nadir after prostatectomy.

Eight PET-negative regions were confirmed positive on biopsy/surgery which were triggered by local reads based on faint focal uptake (n = 4, mean SUVmax= 5.1), CT/MRI lesions (n = 3; mean size, 0.9 cm), or clinical suspicion (n = 1).

PET-directed focal therapy led to a PSA decline of ≥ 50% in 31 of 39 (80%) patients (PET true-positive).

2.6.5.3.2. Impact on patient management – BCR

Studies evaluating impact of 68Ga-PSMA-11 on patient management in the population with BCR are summarized in the table below.

Table 10: Clinical impact in PC patient management from published literature (Restaging)

Reference Country	No. of Patients Enrolled / Analysed	Method of assessment	Pre-PET stage changed after ^{68}Ga-PSMA-11 PET/CT	Intended change in therapy	Implemented change in therapy
Restaging					

Reference Country	No. of Patients Enrolled / Analysed	Method of assessment	Pre-PET stage changed after ^{68}Ga-PSMA-11 PET/CT	Intended change in therapy	Implemented change in therapy
Fendler et al (2020) (USA)	635 / 382 / 206	Questionnaires	NA	260/382 (68%)	160/206 (78%)
Bianchi et al (2019) (IT)	276 / 276	Multidisciplin team	NA	Major:177/276 (64.1%) Minor: 7/276 (2.5%)	NA
Deandreis et al (2020) (IT)	223 / 223	Tumor board evaluation	NA	NA	77/223 (34.5%)
Hope et al (2017) (USA)	150 / 126	Questionnaires	NA	Major: 67/126 (53.2%) Minor: 8/126 (6.4%)	NA
Calais et al (2018) (USA)	161 / 101	Questionnaires	NA	62/101 (61%)	54/101 (53%)
van Leeuwen et al (2016) Australia	300 / 70	2 radiation oncologists' assessment recorded in database	NA	NA	20/70 (28.6%)
Roach et al (2018) Australia	431 / 312	Questionnaires	Disease state: More extensive: 158/312 (51%) Less extensive: 30/312 (10%) Unchanged: 89/312 (29%) Unsure/equivocal: 32/312 (10%) Not answered: 3/312 (1%)	192/312 (62%)	NA
Sonni et al (2020) (USA)	197 / 165	Questionnaires	38-86%	NA	40-72%

*based on first-line imaging

In the eight studies focused on restaging of patients, the intended patient management change ranged from 59.5% to 68% of patients (Hope et al 2017, Calais et al 2018, Roach et al 2018, Bianchi et al 2019, Fendler et al 2020) and from 28.6% to 78% for implemented management change (van Leeuwen et al 2016, Calais et al 2018, Deandreis et al 2020, Fendler et al 2020, Sonni et al 2020).

2.6.5.4. Evidence of efficacy – 68Ga-PSMA-11 PET for patient selection prior to PSMA-targeted treatment

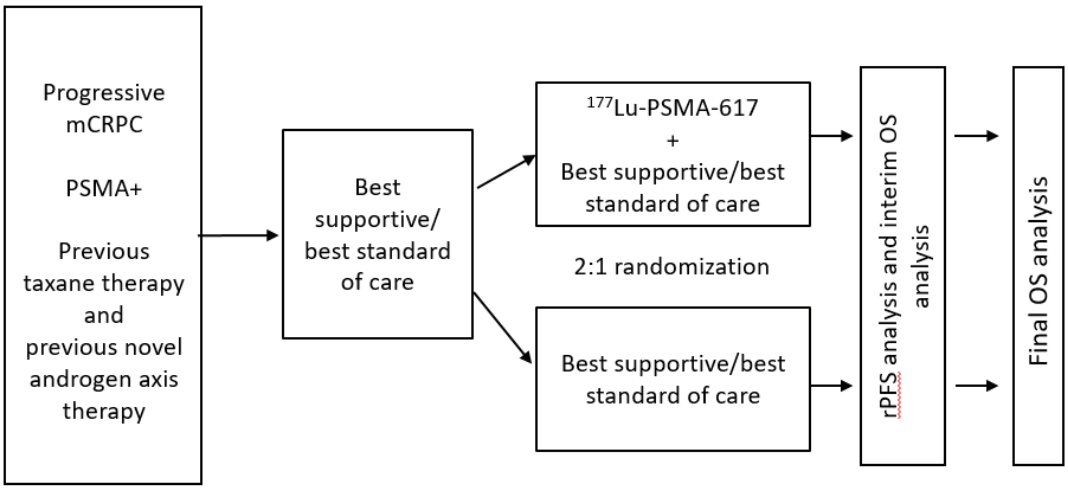
PSMA-617-01 - VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)

Methods

[Study PSMA-617-01] was a Phase III, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to Best supportive care/best standard of care (BSC/BSoC) as compared to BSC/BSoC alone.

68Ga-PSMA-11 PET/CT was applied in the study with the aim to select study participants with PSMA-positive PCa for the subsequent PSMA-targeted treatment with ^{177}Lu-PSMA-617.

Figure 7: Design of Study PSMA-617-01



- **Study Participants**

Study participants were adult male patients who had a histological, pathological, and/or cytological confirmation of PC, progressive mCRPC (based on any one of the following as defined by the prostate cancer clinical trials working group 3 (PCWG3) criteria for clinical trial entry: serum PSA progression, soft-tissue progression, or progression of bone disease), had received at least 1 novel androgen axis drug (NAAD), were previously treated with at least 1 but no more than 2 prior taxane regimens and had a positive 68Ga-PSMA-11 PET/CT scan, as determined by the Sponsor's central reader.

Patients with previous treatment with any of the following within 6 months of randomization: strontium-89, samarium-153, rhenium-186, rhenium-188, radium-223, or hemi-body irradiation or previously treated with PSMA-targeted targeted radioligand therapy (RLT), or any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy) within 28 days prior to day of randomization were excluded.

Baseline 68Ga-PSMA-11 PET/CT scan was done within 4 weeks (+ 2 weeks) prior to C1D1 but not within 6 days prior C1D1.

The Sponsor's central reader review of 68Ga-PSMA-11 PET/CT scans determined eligibility for study inclusion based upon the following criteria:

1. At least one 68Ga-PSMA-11 positive lesion. A PET/CT "positive" lesion was defined as having uptake greater than normal liver parenchyma, whereas a "negative" lesion were those tumours with uptake less than or equal to liver uptake.

2. All lymph nodes that measured ≥ 2.5 cm in short axis had to be 68Ga-PSMA-11 positive.

3. All bone metastases with soft tissue component ≥ 1.0 cm in short axis had to be 68Ga-PSMA-11 positive (patients with PSMA-negative osseous metastases without a soft tissue component, were not to be excluded).

4. All solid organ metastases (e.g. lung, liver, adrenal glands, etc) ≥ 1.0 cm in short axis had to be 68Ga-PSMA-11 positive.

Only patients with at least one PSMA-positive lesion identified on PSMA-PET (i.e. criterion 1) and no negative lesions (i.e. criteria 2-4) were to be enrolled in the study, provided all other inclusion/exclusion criteria were met.

Definition of PSMA scan-positive and PSMA scan-negative lesions were:

- A lesion was considered PSMA scan-positive if the uptake was greater than that observed in the normal liver by visual assessment. The lesion could be present in any organ system (e.g. lymph nodes, skeleton, lung, liver). There was no minimum size requirement for the lesion.
- A lesion was considered PSMA scan-negative if the activity was equal to or less than the normal liver by visual assessment.

An independent imaging review took place.

- **Treatments**

68Ga-PSMA-11 was used only once during screening to select patients for inclusion into the study, as a single i.v. injection over 10-20 seconds at a dose of 111-185 MBq (3-5 mCi) followed by a saline infusion. Low-dose CT transmission scans, in accordance with site's standard of care, were performed in conjunction with the PET scans. The recommended anatomical coverage of the images was skull base to mid-thigh. Patients were imaged 50-100 minutes post 68Ga-PSMA-11 injection. At some centers, furosemide administration was the standard of care to promote elimination of any residual activity in the urinary system.

Different processes were used in the preparation of ^{68}Ga-PSMA-11 doses (one kit-based process and the others as an automatic module-based process) resulting in multiple formulations of ^{68}Ga-PSMA-11 prepared as ready-to-use solutions for injection in the USA, and in Europe.

^{68}Ga-PSMA-11 doses were supplied:

- Via kits from ANMI/Telix/Kyzeo
- Via IND held by institutions for ^{68}Ga-PSMA-11
- Via IMPD held by institutions for ^{68}Ga-PSMA-11

As study (anti-neoplastic) treatments the patients received ^{177}Lu-PSMA-617 in addition to BSC/BSoC or BSC/BSoC alone. ^{177}Lu-PSMA-617 was administered as a slow i.v. injection at a dose of 7.4 GBq (±10%) once every 6 weeks (±1 week) for a maximum of 6 cycles. BSC/BSoC was prescribed by each patient's physician and reflected standard interventions available to clinicians. BSC/BSoC regimen could be adapted.

- **Objectives**

The primary objective of this study was to compare the efficacy of PSMA-targeted treatment - ^{177}Lu-PSMA-617 added to BSC/BSoC compared with patients treated with BSC/BSoC alone in patients with progressive PSMA-positive mCRPC. No specific objective in relation to 68Ga-PSMA-11 PET was defined. It was assumed, that in case of positive outcome for ^{177}Lu-PSMA-617 successful selection of patients by means of 68Ga-PSMA-11 PET could be concluded.

- **Outcomes/endpoints**

Efficacy in the traditional sense (e.g., diagnostic performance, technical performance) of ^{68}Ga-PSMA-11 PET was not evaluated in this study. Positive outcome of the study was to be indirectly concluded as a successful patient selection by means of 68Ga-PSMA-11 PET. Efficacy of ^{177}Lu-PSMA-617 in the study was assessed based on the two alternate endpoints (primary endpoint), radiographic progression-free survival (rPFS) and overall survival (OS) and compared ^{177}Lu-PSMA-617+BSC/BSoC versus BSC/BSoC only.

Exposure and safety data were collected directly for ^{68}Ga-PSMA-11.

A 68Ga-PSMA-11 treatment emergent adverse event (TEAE) was defined as an AE occurring on the date of 68Ga-PSMA-11 dosing and/or up to 6 days after the date of 68Ga-PSMA-11 dosing as long as prior to the first dose of ^{177}Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm. AEs reported as at least "possibly" related to 68Ga-PSMA-11 after the 6-day reporting window but before the initiation of randomized treatment were also 68Ga-PSMA-11 TEAEs.

For patients who were dosed with 68Ga-PSMA-11 but were not randomized, AE monitoring continued up to and including 6 days after administration of 68Ga-PSMA-11.

- **Sample size**

No sample size calculation in relation to the 68Ga-PSMA-11 PET has been done.

- **Randomisation and Blinding (masking)**

Eligible patients were randomized in a 2:1 ratio to receive treatment with either ^{177}Lu-PSMA-617 plus BSC/BSoC or BSC/BSoC alone. All patients underwent 68Ga-PSMA-11 PET. This was an open-label study.

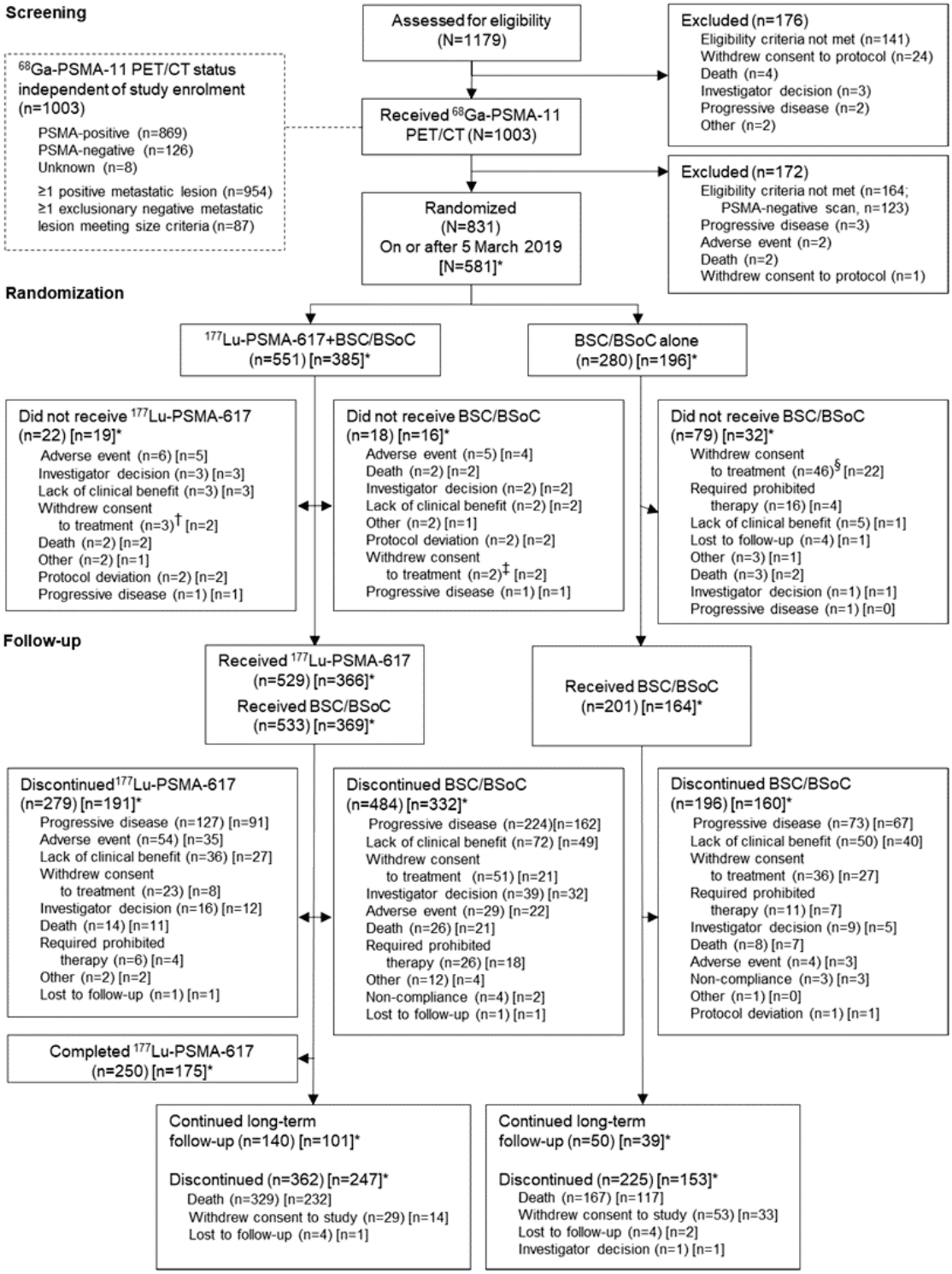
- **Statistical methods**

PSMA-11 Safety Analysis Set was used for the analyses of ^{68}Ga-PSMA-11 data (exposure and safety) and included all patients who received a dose of 68Ga-PSMA-11, including those not randomised. Exposure and safety were summarized in descriptive manner.

Results

- **Participant flow**

Figure 8: Flow of the patients from screening to the C1D1 of the randomised treatment



* Number in square brackets indicate patients randomized on or after 05-Mar-2019, see [Study PSMA-617-01- Section 9.2].
† Reasons for withdrawal of consent to treatment: none given (n=2), travel or procedure "fatigue" (n=1)

‡ Reasons for withdrawal of consent to treatment: none given (n=1), travel or procedure "fatigue" (n=1)
§ Reasons for withdrawal of consent to treatment: receiving BSC/BSoC without ^{177}Lu-PSMA-617 (n=31), none given (n=7), decided to pursue off-study treatment (n=5), travel or procedure "fatigue" (n=2), perceived lack of benefit (n=1)
"Completed ^{177}Lu-PSMA-617" indicates completed at least 4 cycles as reported by the investigator; Source [Study PSMA 617-01-Figure 10.1].

Out of 1179 screened patients, 1003 underwent a ^{68}Ga-PSMA-11 PET/CT scan (between 50-100 minutes post-injection of a mean dose of 167 MBq (4.5 mCi), ranging from 92.8-287.5 MBq (2.5-7.8 mCi)), and 831 patients, who fulfilled the scan interpretation criteria for eligibility (i.e., with ^{68}Ga-PSMA-11 PET/CT positive for eligibility) plus met all other inclusion/exclusion criteria and were randomized to Study PSMA-617-01.

- **Recruitment**

First patient first visit occurred on 29-May-2018 with 1179 patients screened at 82 sites in 10 countries.

- **Conduct of the study**

In total 8 protocol amendments (Amendments 1.1, 1.2, 2.0, 3.0, 4.0, 4.1, 4.2, 4.3), partly specific for individual countries were introduced. Relevant protocol Amendment for this application was the amendment 4.0 (08-Jul-2019):

- Additional imaging analyses details were added for 68Ga-PSMA-11 scan data and the role of the Independent Review with reviewer variability assessment, as well as Quantitative Analysis was added to assess tumour burden and tumour characteristics with rPFS, OS, and other response measures, as determined by PCWG3 criteria.

- Further clarification on the start and end timing for 68Ga-PSMA-11 TEAEs, ^{177}Lu-PSMA-617 TEAEs and BSC/BSoC dosing and intervention TEAEs.

On 20-Sep-2020, a global clinical services provider was impacted by a cyber-security incident. This presented a potential GCP serious breach as certain safety alerts were not being sent to sites, e.g. Columbia Suicide Severity Rating Scale (e-CSSRS) and cardiac safety alerts. Novartis conducted an independent impact assessment of the incident and concluded that this incident did not have an impact on patient safety, data integrity or data privacy. As a result, Novartis did not consider this incident a serious breach.

- **Baseline data**

Overall, a total of 831 patients were randomized and included in the FAS population; 75.3% of whom were ≥ 65 years and 92.4% had an ECOG PS score of 0-1. The median time since initial diagnosis was 7.4 years (range: 0.7, 28.9), almost all (96.3%) had at least one PC-related surgery (including biopsies), and 43.2% had received therapeutic surgery. The majority of patients (76.1%) also had at least one PC-related radiotherapy, and 79.1% had received more than 3 different regimens of prior systemic therapy. All patients had received prior taxane treatment and a prior AR pathway inhibitor. There was a low representation of patients who were Black or African American (6.6% of patients overall) or Asian (2.4%). However, this was balanced between the two treatment arms. Baseline demographic characteristics were similar across treatment groups.

Baseline disease characteristics for the FAS population are presented in table below.

Table 11: Baseline disease characteristics (FAS)

	^{177}Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Time since initial cancer diagnosis (years)			
n	551	280	831
Mean (SD)	8.3 (5.5)	8.9 (5.8)	8.5 (5.6)
Median	7.4	7.4	7.4
Min-Max	0.9-28.9	0.7-26.2	0.7-28.9
Initial histopathological classification, n (%)			
Adenocarcinoma	497 (90.2)	258 (92.1)	755 (90.9)
Neuroendocrine	1 (0.2)	0	1 (0.1)
Unknown	47 (8.5)	20 (7.1)	67 (8.1)
Other	6 (1.1)	2 (0.7)	8 (1.0)
Initial histopathological grade, n (%)			
Grade 1	11 (2.0)	2 (0.7)	13 (1.6)
Grade 2	7 (1.3)	5 (1.8)	12 (1.4)
Grade 3	38 (6.9)	11 (3.9)	49 (5.9)
Grade 3-4	15 (2.7)	10 (3.6)	25 (3.0)
Grade 4	53 (9.7)	33 (11.8)	86 (10.4)
Grade 5	63 (11.5)	38 (13.6)	101 (12.2)
Unknown	361 (65.9)	181 (64.6)	542 (65.5)
Initial Gleason score, categorized, n (%)			
2-3	4 (0.7)	0	4 (0.5)
4-7	181 (32.8)	86 (30.7)	267 (32.1)
8-10	324 (58.8)	170 (60.7)	494 (59.4)
Unknown	42 (7.6)	24 (8.6)	66 (7.9)
Staging at initial diagnosis, n (%)			
I	9 (1.6)	3 (1.1)	12 (1.5)
IA	0	1 (0.4)	1 (0.1)
IB	3 (0.5)	4 (1.4)	7 (0.8)
II	26 (4.7)	10 (3.6)	36 (4.4)
IIA	19 (3.5)	8 (2.9)	27 (3.3)
IIB	22 (4.0)	11 (3.9)	33 (4.0)
III	25 (4.6)	11 (3.9)	36 (4.4)
IIIA	23 (4.2)	9 (3.2)	32 (3.9)
IIIB	38 (6.9)	14 (5.0)	52 (6.3)
IIIC	2 (0.4)	5 (1.8)	7 (0.8)
IV	73 (13.3)	44 (15.8)	117 (14.1)
IVA	10 (1.8)	6 (2.2)	16 (1.9)
IVB	21 (3.8)	13 (4.7)	34 (4.1)
Unknown	277 (50.5)	140 (50.2)	417 (50.4)
Baseline target lesions, n (%)			
Yes	279 (50.6)	140 (50.0)	419 (50.4)
No	272 (49.4)	140 (50.0)	412 (49.6)
Baseline non-target lesions, n (%)			
Yes	429 (77.9)	212 (75.7)	641 (77.1)
No	122 (22.1)	68 (24.3)	190 (22.9)
Total sum of target lesion diameters (mm)			
n	279	140	419
Mean (SD)	58.5 (46.4)	58.6 (44.9)	58.5 (45.9)
Median	45.0	46.2	45.0
Min-Max	10-351	10-249	10-351
Site of disease (target and non-target lesions), n (%) [1]			
Lung			
Yes	49 (8.9)	28 (10.0)	77 (9.3)
No	502 (91.1)	252 (90.0)	754 (90.7)
Liver			
Yes	63 (11.4)	38 (13.6)	101 (12.2)
No	488 (88.6)	242 (86.4)	730 (87.8)
Lymph node			

	^{177}Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Yes	274 (49.7)	141 (50.4)	415 (49.9)
No	277 (50.3)	139 (49.6)	416 (50.1)
Bone			
Yes	504 (91.5)	256 (91.4)	760 (91.5)
No	47 (8.5)	24 (8.6)	71 (8.5)
Baseline PSA doubling time (months) [2]			
n	269	131	400
Mean (SD)	3.2 (5.3)	4.3 (9.1)	3.6 (6.8)
Median	2.4	2.6	2.4
Min-Max	0.0-74.4	0.0-93.1	0.0-93.1
Baseline PSA doubling time (categorized), n (%)			
Stable, non-increasing or decreasing	8 (3.0)	4 (3.1)	12 (3.0)
≤ 6 months	245 (91.1)	115 (87.8)	360 (90.0)
> 6 months	16 (5.9)	12 (9.2)	28 (7.0)
Baseline PSA (ng/mL)			
n	551	280	831
Mean (SD)	288.4 (675.8)	387.6 (937.0)	321.8 (774.6)
Median	77.5	74.6	76.0
Min-Max	0-6988	0-8995	0-8995
Baseline ALP (IU/L)			
n	547	278	825
Mean (SD)	153.7 (183.7)	150.3 (168.1)	152.6 (178.5)
Median	105.0	94.5	101.0
Min-Max	17-2524	28-1355	17-2524
Baseline LDH (IU/L)			
n	550	279	829
Mean	286.4 (283.9)	297.5 (261.7)	290.1 (276.6)
Median	221.0	224.0	223.0
Min-Max	88-5387	105-2693	88-5387

[1] Bone site of disease was based on data collected on target and/or non-target lesion or bone scan assessments.
[2] Baseline PSA doubling time was derived for each patient as the natural log 2 divided by the sum of the fixed and random slopes of the random coefficient linear model between natural log of PSA and time of PSA measurement (in months). Patients with at least 3 PSA values prior to and at the time of screening were included in the model.
Source: Table 14.1.8.1

	^{177}Lu-PSMA-617 +BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Patients with at least 1 prostate cancer-related surgery (including biopsies), n (%) [1]	529 (96.0)	271 (96.8)	800 (96.3)
Prior number of prostate cancer-related surgeries / biopsies			
n	529	271	800
Mean (SD)	1.4 (0.8)	1.4 (0.9)	1.4 (0.8)
Median	1.0	1.0	1.0
Min-Max	1-6	1-8	1-8
Reason for surgery, n (%) [2]			
Diagnostic/biopsy	355 (64.4)	181 (64.6)	536 (64.5)
Therapeutic	236 (42.8)	123 (43.9)	359 (43.2)
Palliative	23 (4.2)	13 (4.6)	36 (4.3)
Other	3 (0.5)	0	3 (0.4)
Patients with at least one prostate cancer-related radiotherapy, n (%)	415 (75.3)	217 (77.5)	632 (76.1)

	^{177}Lu-PSMA-617 +BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Prior number of prostate cancer-related radiotherapies			
n	415	217	632
Mean (SD)	2.1 (1.4)	2.1 (1.4)	2.1 (1.4)
Median	2.0	2.0	2.0
Min-Max	1-11	1-9	1-11
Prior systemic therapy Number of regimens			
n	551	280	831
Mean (SD)	5.2 (2.0)	5.4 (2.2)	5.3 (2.1)
Median	5.0	5.0	5.0
Min-Max	1-10	2-10	1-10
Prior number of taxane-containing regimens			
n	551	280	831
Mean (SD)	1.4 (0.5)	1.5 (0.5)	1.4 (0.5)
Median	1.0	1.0	1.0
Min-Max	1-3	1-3	1-3
Prior number of NAAD-containing regimens			
n	551	280	831
Mean (SD)	1.5 (0.7)	1.6 (0.7)	1.6 (0.7)
Median	1.0	2.0	1.0
Min-Max	1-5	1-4	1-5
Reason for therapy, n (%)			
Therapeutic	424 (77.0)	215 (76.8)	639 (76.9)
Adjuvant	173 (31.4)	87 (31.1)	260 (31.3)
Unknown	109 (19.8)	49 (17.5)	158 (19.0)
Neo-adjuvant	77 (14.0)	47 (16.8)	124 (14.9)
Maintenance	48 (8.7)	27 (9.6)	75 (9.0)
Prophylaxis	15 (2.7)	9 (3.2)	24 (2.9)
Other	11 (2.0)	4 (1.4)	15 (1.8)

[1] All patients had histological, pathological, and/or cytological confirmation of prostate cancer. Not all patients had biopsy details available to be included as part of prior-cancer related surgery data collection.
[2] A patient may be counted in several rows for reason for surgery.

All patients (100%) received at least 1 concomitant medication. Concomitant medications were balanced between the 2 randomized arms, with differences that were typically < 10% with the exception of (^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm):

- Serotonin (5HT3) antagonists: 51.2% vs. 18.0% (mainly ondansetron: 49.7% vs. 16.6%)
- Anti-androgen: 34.6% vs. 48.3% (mainly enzalutamide, 29.9% vs. 42.9%)

- **Numbers analysed**

Assessed for eligibility: N=1179; Received 68Ga-PSMA-11 PET/CT: N=1003; 172 were excluded from randomized treatment, mainly because they failed to meet eligibility criteria for randomization (N=164, including 123 patients with negative 68Ga-PSMA-11 PET/CT scan per the exclusionary read rules); Total Randomized: N=831 (on or after 05-Mar-2019: N=581); Randomized to ^{177}Lu-PSMA-617+BSC/BSoC: N=551 (on or after 05-Mar-2019: N=385); Randomized to BSC/BSoC only: N=280 (on or after 05-Mar-2019: N=196).

- **Outcomes and estimation**

The study met its primary objective, demonstrating a statistically significant improvement in rPFS based on BICR per PCWG3 criteria for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC compared to patients receiving BSC/BSoC only (PFS-FAS; stratified log-rank test $p < 0.001$, one-sided). There was an estimated 60% risk reduction of radiographic disease progression or death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR=0.40; 99.2% CI: 0.29, 0.57).

Data on exposure and safety (AEs) for 68Ga-PSMA-11 are summarised in the safety part of this report.

PSMA-617-01 Reviewer study

Study PSMA-617-01 Reviewer Variability was an independent study of the Study PSMA-617-01 scans to assess the extent of inter-reader variability and intra-reader reproducibility of the 68Ga-PSMA-11 PET/CT scans that were used in Study PSMA-617-01 (VISION study).

Statistics

This study was designed to test the null hypothesis that the Fleiss' Kappa agreement rate between the three independent readers was ≤ 0.52 (Table below, Landis and Koch 1977). The power and sample size calculations were conducted using the KappaSize R package. Based on a 2-sided alpha = 0.05 significance level, a sample size of 125 subjects would provide approximately 85% power, assuming the true Kappa agreement rate was approximately 0.70. Out of the 125 cases, 50 (40%) were exclusion cases, and 75 (60%) were inclusion cases, which deviated from the approximately 85% inclusion case distribution in VISION study. This was intended as, otherwise, the same distribution would have resulted in less than 20 exclusion cases in the study, which was considered inadequate to generate robust outcomes. The selected inclusion/exclusion prevalence distribution resulted in simple agreement rates of 0.77 and 0.85 for the Kappa agreement rates of 0.52 and approximately 0.70, respectively. In the Fleiss Kappa analysis, an overall average agreement rate (Pbar) was also calculated by taking the average of the agreement rate among the three readers for each of the 125 cases.

Table 12: Interpretation of Fleiss' Kappa

Kappa	Interpretation
< 0	Poor agreement
0.01 - 0.20	Slight agreement
0.21 - 0.40	Fair agreement
0.41 – 0.60	Moderate agreement
0.61 - 0.80	Substantial agreement
0.81 - 1.00	Almost perfect agreement

Source: (Landis and Koch 1977)

Reading procedures

Visual assessment was retrospectively performed in a blinded fashion by three independent and experienced readers on a subset of 68Ga-PSMA-11 PET/CT scans and corresponding diagnostic CT/MRI scans from Study PSMA-617-01.

During the blinded read, each reader was assigned a unique randomized read order and instructed to record his visual assessment of each image using the eCRF, resulting in the assessment of each case as either eligible (inclusion case) or ineligible (exclusion case) for enrollment. The criteria used for patient selection in VISION study (see above) were applied.

Accordingly, the following 5 questions were to be responded by each reader during image interpretation:

1. Does the subject have at least one PSMA positive lesion (greater than the liver)? (Yes/No)

2. Is there at least one lymph node ≥2.5 cm (25 mm) in short axis that is PSMA-negative? (Yes/No)

3. Is there at least one bone lesion metastasis with soft tissue component ≥1.0 cm (10 mm) in short axis that is PSMA-negative? (Yes/No)

4. Is there at least one solid organ metastasis ≥1 cm (10 mm) in short axis that is PSMA negative? (Yes/No)

5. Does the subject meet the criteria: Is there at least one PSMA positive-lesion and no PSMA-negative lesion of evaluable size? (Yes/No)

A total of 125 cases were randomly selected, including 75 cases from enrolled patients (inclusion cases) and 50 cases from patients who were excluded from enrollment based on the Study PSMA-617-01 read criteria (exclusion cases). Twenty of the 125 [68Ga]Ga-PSMA-11 PET/CT scans (including 12 inclusion and 8 exclusion cases) and corresponding diagnostic CT/MRI scans were randomly selected and recoded for repeat reads in preparation of the intra-reader reproducibility assessment.

Results

Overall inter-reader variability

Among the 125 cases, the three independent readers completely agreed on the assessment of 96 cases (77%), of which 76 (79%) were scored as inclusion cases and 20 (21%) were scored as exclusion cases. Disagreement was found in 29 cases (23%), with varying combination of concordance observed between the three readers.

Of the 29 discordant cases, the readers differed in their assessment on lymph node in 6 cases, bone metastasis, liver, or cases with no positive lesion in 5 cases each. The remaining 9 cases included lesions in prostate and other locations. Some cases belonged to multiple categories of disagreement.

Fleiss' Kappa statistical analysis was performed to assess inter-reader variability (Fleiss 1971). The overall average agreement rate (Pbar) between all three readers was 0.85. The Kappa value was 0.60 (95% CI, 0.50 to 0.70), indicating moderate to substantial agreement (Landis and Koch 1977). Notably, the lower limit of the 95% confidence interval observed (0.50) represents the midrange of moderate agreement (0.41-0.60), whereas the upper limit of the 95% confidence interval (0.70) represents the midrange of substantial agreement (0.61-0.80).

In addition, an agreement rate of 88% was observed among inclusion cases, compared to 60% among exclusion cases.

Pairwise inter-reader variability analysis

Cohen's Kappa statistical analysis was performed to assess the pairwise inter-reader agreement. The agreement rate of each pairwise analysis was 0.82, 0.88 and 0.84, and the corresponding Cohen's Kappa was 0.54 (95% CI, 0.38-0.71), 0.67 (95% CI, 0.52-0.83) and 0.59 (95% CI, 0.43-0.75) respectively. The observed Cohen's Kappa values represented moderate to substantial agreement between all three pairs of readers, consistent with the results of the Fleiss' Kappa statistics in the overall inter-reader variability analysis.

Intra-reader reproducibility analysis

Of the 125 cases, a randomly selected subset of 20 cases were recoded and read twice by all three readers. Cohen's Kappa statistical analysis was performed to assess the agreement between the repeated reads for each reader. The agreement rate was 0.90, 0.90 and 0.95, and the corresponding Cohen's Kappa was 0.78 (95% CI, 0.49-0.99), 0.76 (95% CI, 0.46-0.99) and 0.89 (95% CI, 0.67-0.99) respectively. The observed Cohen's Kappa values represented substantial to almost perfect agreement for all three readers (Landis and Koch 1977).

Comparison of reader variability study read results and VISION eligibility read results

The reader variability study read results from the three independent readers were compared to the VISION eligibility read results used to determine patient enrollment into the study. Agreement rate was defined as the percentage of actual inclusion cases in VISION out of the cases assessed as inclusion by each reader in the variability study. The agreement rate observed for each reader was 0.76, 0.80 and 0.76 respectively (Table below)

Table 13: Agreement between reader variability study read results and VISION eligibility read results

	Reader 1	Reader 2	Reader 3
Number of inclusion cases assessed by reader in this reader variability study	93	88	96
Number of actual inclusion cases in VISION among the inclusion cases assessed by reader	71	70	73
Number of actual exclusion cases in VISION among the inclusion cases assessed by reader	22	18	23
Agreement rate defined as proportion of actual VISION inclusion case out of the inclusion cases assessed by each reader (95% CI)	0.76 (0.66, 0.85)	0.80 (0.70, 0.87)	0.76 (0.66, 0.84)

PSMA-617-01 - Quantitative analysis of 68Ga-PSMA-11 PET images

Association between imaging data from quantitative PSMA imaging parameters at baseline [^{68}Ga]Ga-PSMA-11 PET/CT scans of patients who had received [^{177}Lu]Lu-PSMA-617 and their clinical outcomes was assessed.

Imaging data meeting quality requirements were analyzed. PSMA expression was quantified by 5 PET parameters: PSMA+ lesions by anatomical region, mean standardized uptake value (SUVmean), maximum SUV (SUVmax), PSMA+ tumor volume, and tumor load (PSMA+ tumor volume × SUVmean). These parameters were extracted from different anatomical regions for each patient, including bone, liver, lymph nodes and soft tissues. Imaging data for the whole body was represented by the combination of all segmented lesions.

Association between PET parameters and radiographic progression-free survival (rPFS), overall survival (OS), objective response rate (ORR), and prostate–specific antigen 50 (PSA50) response was assessed.

Most patients (92.7%) had PSMA uptake in bone. In both the whole-body and regional analyses, statistically significant associations of PSMA PET parameters to clinical outcomes were observed. Higher whole-body SUVmean was associated with improved clinical outcomes; patients in the highest SUVmean quartile had a median rPFS and OS of 14.1 and 21.4 months, vs 5.8 and 14.5 months for those in the lowest quartile, respectively. Absence of PSMA+ lesions in bone, liver, and lymph node, and lower PSMA+ tumor load, were indicators of good prognosis.

2.6.5.5. Inter- and intra-reader variability – Primary staging and BCR

Data from published studies

A summary of the κ values from the articles submitted are listed below.

Inter-reader agreement at whole body level and per location/type of metastases has been summarised.

Table 14: Inter-reader variability for 68Ga-PSMA-11 PET/CT scans in literature

	Read rules used	Number and experienced readers	Patient population (staging and number of scans)	Coefficient values (with 95% CI)	Range/ Landis & Koch strength of reliability
Fanti et al 2017	Assessed 5 sites of disease: Local (prostatic fossa and surgical anastomosis) Pelvic lymph nodes Distant lymph nodes (any other than pelvic) Bone (any skeletal finding) Other (parenchymal organs and any other soft tissues). All areas of increased uptake reported as **anomalous** All anomalous findings suggestive of recurrent PC (clinical + imaging characteristics) noted as **pathologic** Readers reported exact anatomical localization of finding Agreement calculated with Krippendorff's alpha coefficient	7 expert readers	Biochemical recurrence; n=49	Any site K's alpha anomalous: 0.47 K's alpha pathologic: 0.64 Local site K's alpha anomalous: 0.48 K's alpha pathologic: 0.62 Loco-regional LNs K's alpha anomalous: 0.63 K's alpha pathologic: 0.76 Distant LNs K's alpha anomalous: 0.54 K's alpha pathologic: 0.75 Bone K's alpha anomalous: 0.74 K's alpha pathologic: 0.79 Other sites K's alpha anomalous: 0.67	0.47-0.79 Moderate-substantial

	Read rules used	Number and experienced readers	Patient population (staging and number of scans)	Coefficient values (with 95% CI)	Range/ Landis & Koch strength of reliability
				K's alpha pathologic: 0.60	
Fendler et al 2017a	Recorded SUVmax for 1 diseased target region per T (local), N (nodal), Mb (bone), and Mc (visceral) category. Measured background activity by defining SUVmax and SUVmean Overall agreement: defined as complete agreement of an observer for all categories.	16 readers (various experience)	Biochemical recurrence; n=50	All patients (n=50); Fleiss' Kappa Local (T): 0.62 (0.59 – 0.64) Nodal (N): 0.74 (0.71 – 0.76) Bone (Mb): 0.88 (0.86 – 0.91) Visceral (Mc): 0.46 (0.44 – 0.49) BCR and BCP (n=30) Local (T): 0.51 (0.48 – 0.54) Nodal (N): 0.72 (0.69 – 0.76) Bone (Mb): 0.84 (0.80 – 0.87) Visceral (Mc): 0.48 (0.44 – 0.51)	0.44-0.91 Moderate-almost perfect
Derwael et al 2020	Interpretation based on PROMISE criteria including miTNM staging and lesions miPSMA expression score visual estimation and PSMA-RADS version 1.0 for a given scan. Agreement between observers was almost perfect for miM (extra pelvic LN), substantial for miT (primary tumor), miN (Pelvic LN), PSMA-RADS, and miPSMA (visual assessment) expression score of primary PC lesion and metastases. Agreement was moderate for miPSMA score of positive LNs and detection of PC primary lesions	3 readers (1 resident, 2 very experienced)	Newly diagnosed PC; n=43	Agreement K's alpha miTNM: 0.64 (0.48 – 0.76) miT: 0.64 (0.46 – 0.78) miN: 0.76 (0.56 – 0.91) miM: 0.94 (0.81 – 1.00) PSMA-RADS (0.56 – 0.90)	0.46-1.00 Moderate-almost perfect

	Read rules used	Number and experienced readers	Patient population (staging and number of scans)	Coefficient values (with 95% CI)	Range/ Landis & Koch strength of reliability
Miksch et al 2020	Lesions were classified as local recurrent, lymphatic mets, bone, mets, or other lesions Evaluated on 5 point scale 1. Definitely benign 2. Probably benign 3. Equivocal 4. Probably malignant 5. Definitely malignant Agreement based on malignant vs non-malignant	2 readers +1 adjudicator (10 + years experience); 1 Radiology NM and 1 NM	Post prostatectomy, PSA recurrent PC; n=116	Overall detection rate was 50%. Overall agreement in Cohens Kappa: R1/R2: 0.74 (2 reader agreement). Local: 0.76 Lymphatic: 0.73 Bone sites: 0.58	0.58-0.76 Moderate-substantial
Van Kalmthout et al 2020	Phase 1 For clinical decision making, all PET/CT cases were examined by NM physicians Phase 2 Re-evaluated for for primary endpoint analysis (by 2 readers) Readers evaluated for PET suspicious lymph nodes	Experienced (5+ years, >500 studies) 2 readers for phase 2	Newly diagnosed PC and negative bone scan findings > 10%; n=103	Agreement: k=0.58	Moderate
Basha et al 2019	Visual image interpretation Presence or absence of disease Number of: prostatic lesions regional LN mets distant LN mets	5 expert readers (10+ years)	Newly diagnosed PC; n=173	Visual Image Interpretation Overall; k=0.81 (0.61 - 1.00) Primary tumor; k=0.71 (0.40 – 1.00) Regional LN; k=0.79 (0.70 – 0.87) Distant LN; k=0.77 (0.68 - 0.86) Bone mets; k=0.83 (0.74 – 0.92)	Overall substantial-almost perfect By region 0.40-1.00 Moderate-almost perfect

	Read rules used	Number and experienced readers	Patient population (staging and number of scans)	Coefficient values (with 95% CI)	Range/ Landis & Koch strength of reliability
	bone mets soft tissue mets			Soft tissue; k=0.63 (0.47 – 0.80)	
Lawhn-Heath et al 2019	Readers graded images on 2 point scale: A region was judged positive if at least one lesion in the region had greater uptake than blood pool (lymph nodes), physiologic background activity of an organ (visceral, prostate, and prostate bed lesions), or background bone marrow uptake (bone lesions)	2 NM physicians	Biochemically recurrent PC; 150 total subjects; n=72 for interrater reliability	Cohen's kappa statistic Prostate Bed; k= 0.87 Pelvic lymph nodes; k= 0.81 Soft tissues; k= 0.79 Bones; k= 0.78 Overall; k= 0.70	0.70 – 0.87 Substantial-almost perfect
VISION	Vision reads rules Readers identified a single positive lesion Determined if subjects had a single negative lesions meeting criteria for exclusion	3 experienced readers (2 radiology NM, and one NM)	mCRPC; n=125	Fleiss' Kappa = 0.60 (0.50 – 0.70) Cohen's Kappa = 0.78, 0.76, 0.89 for each reader	0.50-0.60 Moderate-substantial 0.76-0.89 Almost perfect

K=kappa, LN= Lymph Nodes, NM= Nuclear Medicine

- **Summary of main efficacy results**

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

Table 15: Summary of efficacy for studies by van Kalmthout et al 2020 and Hope et al., 2021 (Diagnostic performance, and impact on patient management and inter-reader agreement – primary staging), and Fendler et al 2019 (PPV and inter-reader variability - BCR)

Title: Prospective Validation of Gallium-68 Prostate Specific Membrane Antigen-Positron Emission Tomography/Computerized Tomography for Primary Staging of Prostate Cancer			
Study identifier	Dutch Trial Register: NTR6830 Reference: **van Kalmthout** L, van Melick HE, Lavalaye J, et al (2020) Prospective validation of gallium-68 prostate specific membrane antigen-positron emission tomography/computerized tomography for primary staging of prostate cancer. J Urol; 203(3):537-545.		
Design	A prospective, multicenter, single-arm, study in men with intermediate-risk or high-risk, biopsy-proven prostate cancer		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		There was no fixed duration. Imaging results, read by two independent readers, were compared with a histopathology reference standard at the end of the study. not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Histopathology reference standard		Histopathology of lymph nodes (LN) from an extended pelvic lymph node dissection (ePLND) in men with biopsy-proven prostate cancer and intermediate- and high-risk features indicated for this surgical procedure. Detection of lymph node metastatic disease on ^{68}Ga-PSMA-11 PET/CT imaging. The ground truth regarding presence of metastatic lymph node disease using histopathologic findings. LN specimens were examined by dedicated uropathologists according to ISUP (International Society of Urological Pathology) protocols. 96 enrolled patients
	^{68}Ga-PSMA-11 PET/CT Images		Men with biopsy-proven prostate cancer and intermediate- and high-risk features indicated for ePLND who received ^{68}Ga-PSMA-11 103 enrolled patients
Endpoints and definitions	Primary endpoint	Patient-based sensitivity	The proportion of patients containing true positive lesions on ^{68}Ga-PSMA-11 among those that are standard of truth positive (true positive or false negative).

	Secondary endpoint	Patient-based specificity, positive predictive value (PPV), negative predictive value (NPV)	The proportion of patients containing true negative lesions on ^{68}Ga-PSMA-11 among those that are standard of truth negative (false positive or true negative). The proportion of patients containing at least one true positive ^{68}Ga-PSMA-11 PET lesions, out of all patients with a positive PET scan. The proportion of patients containing at least one true negative ^{68}Ga-PSMA-11 PET lesions, out of all patients with a negative PET scan.
	Secondary endpoint	Patient management impact	Changes in patient management, as a result of the imaging results, were determined by responses from tumor board discussions. Management change was defined by an ePLND cancellation or ePLND template extension.
	Secondary endpoint	Inter-reader agreement	A kappa statistic was performed to assess the agreement rate between 2 reader's determinations for suspicious pathology findings in the prostate region, regional and nonregional lymph nodes, and osseous and visceral lesions according to a 5-point scale.
Database lock	Last patient enrolled: Sept-2018		
Results and Analysis			
Analysis description	**Primary endpoint – Patient-based Sensitivity**		
Analysis population and time point description	All patients who had a ^{68}Ga-PSMA-11 PET/CT and an adequate extended pelvic lymph node dissection were included in the analysis. Time point: N/A		
Descriptive statistics and estimate variability	**Treatment group**	**Histopathology reference standard**	
	Number of evaluable patients	96	
	Sensitivity, % [95%CI]	42% [27, 58]	
Analysis description	**Secondary endpoint – Patient-based Specificity, PPV, NPV**		
Analysis population and time point description	All patients who had a ^{68}Ga-PSMA-11 PET/CT and an adequate extended pelvic lymph node dissection were included in the analysis. Time point: N/A		
Descriptive statistics and estimate variability	**Treatment group**	**Histopathology reference standard**	
	Number of evaluable patients	96	
	Specificity, % [95%CI]	91% [79, 97]	
	positive predictive value (PPV), % [95%CI]	77% [54, 91]	
	negative predictive value (NPV), % [95%CI]	68% [56, 78]	
Analysis description	**Secondary endpoint – Inter-reader agreement**		
Analysis population and time point description	All patients who had a ^{68}Ga-PSMA-11 PET/CT and an adequate extended pelvic lymph node dissection were included in the analysis. Time point: N/A		

Descriptive statistics and estimate variability	**Treatment group**	**Histopathology reference standard**
	Number of evaluable patients	96
	Kappa	0.67
Analysis description	**Secondary endpoint – Patient management impact**	
Analysis population and time point description	All patients who had a ^{68}Ga-PSMA-11 PET/CT were included in the analysis. Time point: N/A	
Descriptive statistics and estimate variability	**Treatment group**	**^{68}Ga-PSMA-11 PET/CT Images**
	Number of evaluable patients	103
	Change in patient management, n (%)	13 (13%)
	ePLND cancelled, n (%)	6 (6%)
	ePLND template extended, n (%)	6 (6%)
	Additional therapy after ePLND, n (%)	1 (7%)

Title: Diagnostic Accuracy of ^{68}Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection: A Multicenter Prospective Phase 3 Imaging Trial		
Study identifier	Clinicaltrials.gov Numbers: NCT03368547, NCT02611882, and NCT02919111 Reference: **Hope** TA, Eiber M, Armstrong WR, et al (2021) Diagnostic Accuracy of ^{68}Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection: A Multicenter Prospective Phase 3 Imaging Trial. JAMA Oncol; 7(11):1635-1642.	
Design	A prospective, multicenter, single-arm, phase 3 study in men with intermediate-risk or high-risk, biopsy-proven prostate cancer	
	Duration of main phase:	There was no fixed duration. Imaging results, read by three independent readers, were compared with a histopathology reference standard at the end of the study.
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority	
Treatments groups	Histopathology reference standard	Histopathology of pelvic lymph nodes from a radical prostatectomy in men with untreated, biopsy-proven prostate cancer and intermediate- and high-risk features indicated for this surgical procedure. Detection of regional nodal metastatic disease on ^{68}Ga-PSMA-11 PET/CT or PET/MRI imaging. The ground truth regarding presence of metastatic disease using histopathologic findings. 277 enrolled patients

Endpoints and definitions	Primary endpoint	Patient-based sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)	The proportion of patients containing true positive lesions on ^{68}Ga-PSMA-11 among those that are standard of truth positive (true positive or false negative). The proportion of patients containing true negative lesions on ^{68}Ga-PSMA-11 among those that are standard of truth negative (false positive or true negative). The proportion of patients containing at least one true positive ^{68}Ga-PSMA-11 PET lesions, out of all patients with a positive PET scan. The proportion of patients containing at least one true negative ^{68}Ga-PSMA-11 PET lesions, out of all patients with a negative PET scan.
	Secondary endpoint	Inter-reader agreement	The Fleiss' kappa statistic was performed to assess the agreement rate between all 3 reader's determinations of PSMA (+) versus PSMA (-) for 3 regions (right-sided nodes, left-sided nodes, other nodes).
Database lock	Last patient enrolled: Dec-2019		
Results and Analysis			
Analysis description	**Primary endpoint – Patient-based Sensitivity, Specificity, PPV, NPV**		
Analysis population and time point description	All patients who had a ^{68}Ga-PSMA-11 PET/CT or PET/MRI and a prostatectomy were included in the analysis. Time point: N/A		
Descriptive statistics and estimate variability	**Treatment group**	**Histopathology reference standard**	
	Number of evaluable patients	277	
	Sensitivity, % [95%CI]	40% [34, 46]	
	Specificity, % [95%CI]	95% [92, 97]	
	PPV, % [95%CI]	75% [70, 80]	
	NPV, % [95%CI]	81% [76, 85]	
Analysis description	**Secondary endpoint – Inter-reader agreement**		
Analysis population and time point description	All patients who had a ^{68}Ga-PSMA-11 PET/CT or PET/MRI and a prostatectomy were included in the analysis. Time point: N/A		
Descriptive statistics and estimate variability	**Treatment group**	**Histopathology reference standard**	
	Number of evaluable patients	277	
	Statistic	Right-sided nodes	Left-sided nodes	Other nodes
	Fleiss Kappa [95% CI]	0.61 [0.55, 0.67]	0.66 [0.60, 0.71]	0.52 [0.46, 0.58]

Title: Assessment of ^{68}Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: A prospective single-arm clinical trial

Study identifier	Clinicaltrials.gov Numbers: NCT02940262 and NCT03353740. Reference: **Fendler** WP, Calais J, Eiber M, et al (2019) Assessment of ^{68}Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: A prospective single-arm clinical trial. JAMA Oncol; 5(6):856-63. Suppl content: doi:10.101/jamaoncol.2019.0096.		
Design	A prospective, multicenter, single-arm study in men with biochemically recurrent prostate cancer		
	Duration of main phase:		There was no fixed duration. Imaging results, read by three members of a pool of nine independent central readers, were compared with either a histopathology reference standard or a composite reference standard at a median follow-up duration of 9 months.
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Histopathology reference standard		Men with histopathologically-proven and biochemical recurrence prostate cancer whom had available a histopathology reference standard alone. 635 randomized patients
	Composite reference standard		Men with histopathologically-proven and biochemical recurrence prostate cancer whom had available a composite reference standard (histopathology, serial serum PSA levels and imaging (CT, MRI, and/or bone scan)) 635 randomized patients
Endpoints and definitions	Primary endpoint	Positive predictive value (PPV) on a per-patient and per-region basis confirmed by histopathology reference standard	The proportion of patients/regions containing at least one true positive ^{68}Ga-PSMA-11 PET lesions, out of all patients/regions with a positive PET scan.
	Secondary endpoint	Sensitivity on a per-patient and per-region basis confirmed by histopathology reference standard	The proportion of patients/regions containing true positive lesions on ^{68}Ga-PSMA-11 among those that are standard of truth positive (true positive or false negative).
	Secondary endpoint	Positive predictive value (PPV) on a per-patient and per-region basis confirmed by composite reference standard	The proportion of patients/regions containing at least one true positive ^{68}Ga-PSMA-11 PET lesions (as confirmed by composite reference standard), out of all patients/regions with a positive PET scan.
	Secondary endpoint	Inter-reader agreement	The Fleiss' kappa statistic was performed to assess the agreement rate between all 3 reader's determinations of PSMA (+) versus PSMA (-) for 4 regions (prostate bed, pelvic nodes, extrapelvic soft tissue, bone)
Database lock	Last patient enrolled: Oct-2017		
Results and Analysis			
Analysis description	**Primary endpoint - Positive predictive value (PPV) confirmed by histopathology reference standard**		
Analysis population and time point description	All patients who had a ^{68}Ga-PSMA-11 PET and detection of tumor location confirmed by histopathology/biopsy were included in the analysis. Time point: N/A		
Descriptive statistics and estimate variability	**Treatment group**	**Histopathology reference standard**	
	Number of evaluable patients	93	

	PPV per-patient [95% CI]	84% [75, 90]			
	PPV per-region [95% CI]	84% [76, 91]			
Analysis description	**Secondary endpoint - Sensitivity confirmed by histopathology reference standard**				
Analysis population and time point description	All patients who had a ^{68}Ga-PSMA-11 PET and detection of tumor location confirmed by histopathology/biopsy were included in the analysis. Time point: N/A				
Descriptive statistics and estimate variability	**Treatment group**	**Histopathology reference standard**			
	Number of evaluable patients	93			
	Sensitivity per patient [95% CI]	92% [84, 96]			
	Sensitivity per region [95% CI]	90% [82, 95]			
Analysis description	**Secondary endpoint - Positive predictive value (PPV) confirmed by composite reference standard**				
Analysis population and time point description	All patients who had a ^{68}Ga-PSMA-11 PET and detection of tumor location confirmed by histopathology/biopsy, serial serum PSA levels and conventional imaging follow-up Time point: N/A				
Descriptive statistics and estimate variability	**Treatment group**	**Composite reference standard**			
	Number of evaluable patients	223			
	PPV per patient [95% CI]	92% [88, 95]			
	PPV per region [95% CI]	92% [88, 95]			
Analysis description	**Secondary endpoint – Inter-reader agreement**				
Analysis population and time point description	Patients who had a ^{68}Ga-PSMA-11 PET Time point: N/A				
Descriptive statistics and estimate variability	**Treatment group**	Not specified			
	Number of evaluable patients	Not specified			
	Statistic	Prostate Bed	Pelvic nodes	Extra-pelvic soft tissue	Bone
	Fleiss Kappa [95% CI]	0.65 [0.61, 0.70]	0.73 [0.69, 0.78]	0.70 [0.65, 0.74]	0.78 [0.73, 0.82]

2.6.5.6. Clinical studies in special populations

There were no studies performed in renal or hepatic impaired patients, or in children. The target population is older and elderly subjects, which were included in the clinical trials. Subgroup analyses per age for safety is described in the Clinical safety section.

2.6.5.7. Analysis performed across trials (pooled analyses and meta-analysis)

Perera et al (2020) performed a meta-analysis of studies evaluating the utility of ^{68}Ga-PSMA PET in the detection of metastatic disease in **high-risk and advanced prostate cancer for primary (prior to**

definitive therapy) or secondary staging (biochemical recurrence following definitive therapy). The mean age from the collective studies ranged from 61-74 years. Across 37 studies that met the relevance criteria, 5 studies reported on the predictive ability of PSMA-PET imaging for primary staging purposes with respect to histology-proven disease. For these 5 studies, summary sensitivity and specificity were calculated as per-lesion and per-patient analyses: summary sensitivity of 75% and summary specificity of 99% (per-lesion analysis); and summary sensitivity 77% and summary specificity 97% (per-patient analysis).

^{68}Ga-PSMA PET improves detection of metastases with biochemical recurrence, particularly at low pre-PET PSA levels of > 0.2 ng/ml (33%) and 0.2–0.5 ng/ml (45%). ^{68}Ga-PSMA-PET produces favorable sensitivity and specificity profiles on meta-analysis of pooled data. This analysis highlighted different anatomic patterns of metastatic spread according to PSMA PET in the primary and biochemically recurrent settings.

Hope et al (2019) performed a systematic review and meta-analysis involving 4149 prostate cancer patients (mean age range: 62-80 years) from 41 publications summarizing studies of **staging or restaging** with ^{68}Ga-PSMA-11 PET/CT or PET/MRI in patients with either localized or metastatic prostate cancer. They further determined the imaging test accuracy of the ^{68}Ga-PSMA-11 PET/CT or PET/MRI method using tissues samples obtained through biopsy or surgery as the reference standard. The meta-analysis of ^{68}Ga-PSMA-11 at initial staging demonstrated a sensitivity and specificity of 0.74 (95% CI: 0.51–0.89) and 0.96 (95% CI: 0.85–0.99), respectively, using nodal pathology at prostatectomy as a gold standard. At biochemical recurrence, the PPV was 0.99 (95% CI: 0.96–1.00). The detection rate was 0.63 (95% CI: 0.55–0.70), with a PSA of less than 2.0 and 0.94 (95% CI: 0.91–0.96) with a PSA of more than 2.0. Doses and uptake times were in similar ranges across studies, with most studies using a dose of 120-230 MBq of ^{68}Ga-PSMA-11 and an imaging time starting approximately 60 min after injection.

Across studies of varying size, aim and design, high sensitivity and specificity were achieved for ^{68}Ga-PSMA-11 PET, suggesting that expanding experience is yielding consistent results among historical and more recent reads.

Perera et al (2016) performed a systematic review and meta-analysis of reported predictors of positive ^{68}Ga-PSMA-11 PET and corresponding sensitivity and specificity profiles. The analysis included 1309 patients with prostate cancer from 16 articles. The median age from the collective studies ranged from 62-73 years.

The overall percentage of positive ^{68}Ga-PSMA-11 PET among patients was 40% (95% CI: 19–64%) for primary staging and 76% (95% CI: 66–85%) for BCR. Positive ^{68}Ga-PSMA-11 PET scans for BCR patients increased with pre-PET PSA. For the PSA categories 0–0.2, 0.2–1, 1–2, and > 2 ng/ml, 42%, 58%, 76%, and 95% scans, respectively, were positive. Shorter PSA doubling time increased ^{68}Ga-PSMA-11 PET positivity. On per-patient analysis, the summary sensitivity and specificity were both 86%. On per lesion analysis, the summary sensitivity and specificity were 80% and 97%, respectively. In the setting of BCR prostate cancer, pre-PET PSA predicts the risk of positive ^{68}Ga-PSMA-11 PET. Pooled data indicated favorable sensitivity and specificity profiles compared to choline-based PET imaging techniques.

2.6.5.8. Supportive study(ies)

In addition to the evidence presented in the sections above, published studies including active comparators/other PET tracers have been submitted. These are briefly summarised in the Table below.

Table 16: Comparison of 68Ga-PSMA PET vs. Other Imaging Methodologies

Reference Comparison Method Indication	Endpoint	^{68}Ga-PSMA	Control	Remark	Conclusions
Wu et al 2019 ^{68}Ga-PSMA PET/CT vs **MRI** Systematic review and meta-analysis Lymph node staging in patients with intermediate- and high-risk PCa			**MRI**		^{68}Ga-PSMA had a higher sensitivity and a similar different specificity in detecting lymph node metastases compared to MRI.
	Pooled sensitivity	0.65 [0.49-0.79]	0.41 [0.26-0.57]		
	Pooled specificity	0.94 [0.88-0.97]	0.92 [0.86-0.95]		
	AUC	0.92	0.83		
Sonni et al 2022 ^{68}Ga-PSMA-11 PET/CT vs **mpMRI** vs **^{68}Ga-PSMA-11 + mpMRI** Histopathology taken as the gold-standard Newly diagnosed patients with intermediate- or high-risk prostate cancer	Lesion-based analysis		**mpMRI**	**combined**	Both ^{68}Ga-PSMA-11 PET/CT and multi-parametric magnetic resonance imaging (mpMRI) performed well in the detection and intraprostatic localization of PCa. mpMRI had superior performance in the definition of T stage. The combination of both techniques improved tumor extent delineation.
	Overall cancer detection rate	85%	83%	87% p=ns	
	Extraprostatic extension (AUC)	0.59	0.79	p=0.002	
	Seminal vesical invasion (AUC)	0.63	0.84	p=0.001	
Zhao et al 2022 ^{68}Ga-PSMA-11 PET/CT vs **^{99m}Tc-MDP**[1] bone scintigraphy Meta-analysis Detection of bone metastases in patients with PCa			**99mTc-MDP**		On a per-patient basis, the diagnostic performance of ^{68}Ga-PSMA-11 PET/CT is superior to that of ^{99m}Tc-MDP bone scintigraphy to detect PCa bone metastases.
	Pooled sensitivity	98% [94-99%]	83% [69-91%]		
	Pooled specificity	97% [91-99%]	68% [41-87%]		
	AUC	0.99	0.85		
Hofman et al 2020 ^{68}Ga-PSMA-11 vs Conventional Imaging (**CT and bone scan**) Original research Newly diagnosed, high-risk biopsy-proven prostate cancer considered for radical treatment			**Conventional Imaging**		^{68}Ga-PSMA-11 provides superior accuracy to the combined findings of CT and bone scanning.
	Accuracy	92% [88–95]	65% [60–69]	p<0·0001	
	Sensitivity	85% [74–96]	38% [24–52]		
	Specificity	98% [95–100]	91% [85–97]		
	Subgroup analyses			**absolute difference**	
	Pelvic nodal metastases AUC of the ROC curve	91%	59%	32% [28–35]	
	Distant metastases	95%	74%	22% [18-26]	
Calais et al 2019 68Ga-PSMA-11 PET/CT vs **^{18}F-Fluciclovine**[2] Original research Patients with BCR (PSA <2.0 ng/ml) after radical prostatectomy	Patient-level analysis		**18F-Fluciclovine**		^{68}Ga-PSMA-11 has higher detection rates, and should be the PET tracer of choice when PET/CT imaging is considered for subsequent treatment management decisions in patients with prostate cancer and biochemical recurrence after radical prostatectomy and low PSA concentrations (≤2.0 ng/mL).
	Overall detection (k statistic)	0.67	0.20	p=0.002	
	Region-level detection				
	Prostate bed	0.65	0.43	p=0.046	
	Pelvic LN	0.76	0.05	p<0.0001	
	Extrapelvic LN	0.60	-0.02	p=0.0025	
	Bone	0.46	-0.03	p=0.0051	
	Other organs	0.65	-0.01	p=0.016	
	Any extrapelvic lesion	0.60	-0.07	p<0.0001	
	Patient-based analysis		**18F-Fluciclovine**		^{18}F-Fluciclovine PET/CT outperforms ^{68}Ga-PSMA-11 in detecting local recurrence, especially when it is located in close anatomical relation to the urinary bladder. For the
	Overall detection rate of PCa recurrence	82.8%	79.3%	p=0.64	
	Local recurrence	27.6%	37.9%	p=0.03	

Reference Comparison Method Indication	Endpoint	^{68}Ga-PSMA	Control	Remark	Conclusions
Pernthaler et al 2019 **^{18}F-Fluciclovine** vs ^{68}Ga-PSMA-11 Original research Lesion identification in patients with BCR	Pelvic LN recurrence	50%	46.6%	p=0.71	remaining locations of disease, both compounds are widely comparable.
	Extrapelvic LN metastases	51.7%	41.4%	p=0.26	
	Bone metastases	36.2%	25.9%	p=0.23	
Morigi et al 2015 ^{68}Ga-PSMA vs **^{18}F-choline**[3] PET/CT Histopathology available for confirmation in 24% of patients Lesion identification in patients with BCR	Patient-based analysis		**18F-choline**	**combined**	In patients with BCR and low PSA levels, ^{68}Ga-PSMA demonstrated a significantly higher detection rate than ^{18}F-choline, and a high overall impact on management.
	Lesion detection of PCa recurrence	37%	3%	29%	
	Lesion-based analysis				
	Number of lesions detected	59	29	p<0.001	
	Management change	63% (24/38 patients), with 54% (13/24) being due to 68Ga-PSMA imaging alone			
Afshar-Oromieh et al 2014 ^{68}Ga-PSMA vs **^{18}F-choline** PET/CT Original research Lesion identification in patients suspected recurrent prostate cancer	Patient-based analysis	**PET/CT**	**18F-choline**		^{68}Ga-PSMA PET/CT can detect prostate cancer lesions with improved contrast when compared to ^{18}F-choline, especially at low PSA levels.
	Overall lesion detection	86.5%	70.3%		
	Lesion-based analysis				
	Number of lesions detected	78	56	p=0.04	
	68Ga-PSMA vs 18F-choline	**>10% higher**	**>10% lower**	**equal**	
	SUVmax	79.1%	15.4%	5.5% p<0.001	
	TBR	94.9%	5.1%	p<0.001	
Treglia et al 2019 PSMA vs **choline** PET/CT Meta-analysis Lesion identification in patients with BCR		**PSMA**	**Choline**		PSMA PET/CT proved to be clearly superior in detecting BCR prostate cancer lesions when compared to choline PET/CT, especially at low PSA levels (≤1 ng/ml).
	Pooled detection rate	78% [70-84%]	56% [37-75%]		
	Pooled detection rate at PSA ≤ 1 ng/ml	54% [43-65%]	27% [17-39%]		
Alberts et al 2020 PSMA-PET vs **^{18}F-Fluciclovine** vs **choline-based radiotracers** Systematic review and network meta-analysis Recurrent prostate cancer	Patient-based detection rate ratio	**18F-Fluciclovine**	**11C-choline**	**18F-choline**	PSMA radiotracers are superior to the other compounds, particularly to choline-based ones.
	68Ga-PSMA-11 vs	2.19 [1.25-4.03]	2.96 [1.68-5.58]	5.44 [2.79-12.91]	

AUC Area under the curve; **ROC** reciever operating characteristic; **TBR** tumor to background ratio; LN lymph nodes

1) ^{99}mTc-MDP target and mechanism of action (MoA): hydroxyapatite of the bone cortex and altered osteogenesis.

2) ^{18}F-Fluciclovine target and MoA: aminoacids and aminoacid transport.

3) Choline target and MoA: cell membrane metabolism and cell membrane synthesis and transmembrane signaling modulation.

2.6.6. Discussion on clinical efficacy

This is essentially a literature-based application. The Applicant addressed around 30 publications in the summary of clinical efficacy.

The updated indication targets 3 clinical situations: primary staging of patients with PCa prior to curative treatment, diagnosis of BCR and selection of patients with metastasized PCa prior to treatment with PSMA-based therapy.

To support the efficacy claims, the Applicant has submitted two study reports describing own clinical data, both based on the same Phase III clinical study PSMA-617-01, and large number of published studies in BCR setting and in primary staging. Additionally, quantitative analysis of 68Ga-PSMA-11 PET images has been provided. Use of literature data in this submission is acceptable. Overall, the amount of the data submitted, and the contents addressed, are acceptable.

General requirement towards new diagnostic methodologies is that these are compared to the available alternatives e.g., in terms of diagnostic performance (Reference is made to the EMA guideline on diagnostic agents CPMP/EWP/1119/98/Rev. 1 and Appendix EMEA/CHMP/EWP/321180/2008). According to the updated indication wording, ^{68}Ga-PSMA-11 PET is expected to be used as imaging prior to curative intent therapy in primary staging, as an alternative to choline, and fluciclovine PET in the diagnosis of PCa recurrence in patients with BCR, and as a identification tool for PSMA-based therapy in patients with metastasized PCa. Respective comparative data of 68Ga-PSMA-11 against the other PET tracers have been provided.

Design and conduct of clinical studies

The submitted clinical studies were designed as prospective or retrospective single, or multiple-site clinical studies, mostly with single treatment arm and not utilizing comparator. Standard of truth (SOT)/standard of reference in the studies in primary staging of PCa was mostly histopathology, which is a universal SOT and accepted. In the studies in BCR mostly composite SOT based on clinical follow-up, findings in other imaging, histopathology, etc. was applied. Depending on the chosen criteria, composite SOTs are acceptable.

Assessment of efficacy was based on evaluating the following aspects: diagnostic performance (sensitivity, specificity, PPV, NPV and accuracy in primary staging, sensitivity and PPV in BCR diagnostics), technical performance (inter-reader variability, semi-quantitative measurements, e.g., SUVmax), and impact on patient management. These are acceptable and in line with the requirements of relevant guideline.

Limitations detected are as follows: all but 3 studies (Fendler et al, Hofman et al and Hope et al) were planned as exploratory studies, validation of impact on patient management did not take place in majority of the studies, methodology of assessment of inter-reader variability in the own study (VISION) is deficient, impact on clinical outcomes has not been evaluated, clinical value of the data from VISION study is limited (diagnostic performance not evaluated, quantitative analysis provides exploratory, partly contradictory, evidence).

Efficacy data and additional analyses

Dose finding

No dedicated dose-response/dose-finding studies were conducted, and the proposed dosing regimen is based on the experience from the majority of the published studies in patients with PCa and the joint recommendations of the EANM and SNMMI procedure guideline for prostate cancer imaging (Fendler et al 2017). This approach is acceptable.

The proposed dose of 68Ga-PSMA-11 is 1.8-2.2 MBq/kg of body weight (0.049-0.059 mCi/kg), with a minimum dose of 111 MBq (3 mCi) and up to a maximum dose of 259 MBq (7 mCi), administered by intravenous injection. The recommended imaging time is at 60 min post injection, with a range of 50 to 100 min post injection.

A standard and maximum recommended activities (150 MBq and 259 MBq) of 68Ga-PSMA-11 result in the effective doses (2.37-3.87 mSv and 6.68 mSv) which are lower than those of other PET agents used for prostate cancer imaging and well within the effective dose from a diagnostic CT. Additionally, the maximum 25 µg mass dose is in the microdose range, as it is ≤ 100 µg and ≤ 1/100th of the nonclinical NOAEL (FDA 2018, EMA 2018). Proposed timing of PET scan (50-100 min after tracer injection) is also in line with the data in the literature.

The minimum and maximum total doses defined correspond to the weight range of 50.5 kg to 144 kg when calculated for the 1.8-2.2 MBq/kg dosing. Depending on the actual time from production of 68GaCl3 required for labelling of gozetotide, large amount of the labelled solution (and respectively higher amount of mass) may be required to achieve adequate activity at the time of injection. Upper limit for the injected volume is, however specified in the SmPC (section 12), that should prevent excessive exposure to gozetotide.

The proposed dose regimen was tested in the study conducted by the Applicant (VISION) and no major safety occurrences have been observed (see clinical safety). The proposed dosing is, thus, acceptable.

Diagnostic performance and impact on patient management - primary staging of PCa

The Applicant has submitted 9 published studies reporting diagnostic performance of 68Ga-PSMA-11 PET in patients with confirmed primary PCa.

The population included in these studies represented the patients with biopsy-confirmed predominantly high-risk PCa scheduled for undergoing primary staging with subsequent curative intent treatment (prostatectomy with or without PLND/ePLND or radiotherapy). This is a typical population that is subjected to primary staging prior to the start of treatment and the key target of staging is to find out whether the cancer has spread to LN, and/or metastasised to other systems/organs and distant locations.

Hofman et al. conducted a prospective controlled multicentre confirmatory study. The primary outcome was accuracy of the 68Ga-PSMA PET compared to conventional imaging (CT and bone scan) in identifying either pelvic nodal or distant metastatic disease in the patients with biopsy-confirmed PCa. Statistical planning and sample size calculation appear acceptable. The study was powered for superiority. Standard of reference was defined based on histopathology or bone scan (hard criteria), or large number of soft criteria (11 in total).

The study showed high levels of sensitivity, specificity and accuracy in detection of pelvic nodal and distant metastases with 68Ga-PSMA-11 PET. Compared to conventional imaging with CT and bone scanning, PSMA PET-CT showed significantly greater accuracy and sensitivity and numerically higher specificity in patient-level analysis. The difference in the accuracy was driven by better sensitivity, particularly in detection of pelvic LN metastases.

Additionally, 68Ga-PSMA PET-CT had fewer equivocal results and lead to lower radiation exposure than CT and bone scan. Impact on patient management in almost third of the population was reported. Whether or not the latter lead to positive clinical outcome is difficult to judge, as validation was missing/no survival analyses was done.

The key limitation of this study is the use of histopathology (reliable SOT) in only 18 of 300 patients. In the remaining patients the combination of soft criteria (composite SOT) was applied. The latter creates uncertainty in the study outcomes as some of the criteria raise concerns in terms of objectivity or robustness. The criteria, such as, typical appearance of multi-focal metastatic disease, appearance of a metastatic lesion on an imaging modality other than the one performed as the index scan and localised treatment for metastasis are not regarded sufficiently objective, or robust to be part of the SOT definition. Especially if used in combination with each other. As, concretely which combinations of soft criteria lead to which results have not been presented, the extent of possible bias on study results from these questionable criteria is difficult to assess.

Further, validation of the findings on first-line imaging (by means of SOT or composite SOT) took place after 6 months follow-up. This time period might have been too short, particularly for adequate assessment of the hard SOT criterion based on bone scan.

Also, either the comparator, or the 68Ga-PSMA PET (repeated imaging) itself was applied for confirmation of the diagnosis which is against the recommendations of the EMA guideline on diagnostic agents.

Evaluation of the images took place in an open-label manner, which may be less appreciated from methodological point of view, but probably reflects the clinical situation more realistically.

Overall, the study provided supportive evidence despite the above mentioned shortcomings questioning the robustness of the data.

Additional evidence was presented from the remaining studies Yaxley et al. and van Kalmthout et al. which appear more robust. Strengths of these studies are the use of histopathology as SOT and acceptable blinded reading procedures. In these studies, diagnostic performance of 68Ga-PSMA-11 PET was quite similar and showed rather low levels of sensitivity and high degree of specificity, with more variable moderate PPV and NPV (sensitivity: 38.2% and 41.5%, specificity; 93.5% and 90.9%, PPV: 67.7% and 77.3%, and NPV: 80.8% and 67.6%). These data are not quite consistent with the literature data (Mottet et al., Hofman et al.), which report higher levels of sensitivity.

The large study conducted by Hope et al., did not reach primary objective. However, diagnostic performance of 68Ga-PSMA-11 PET was similar to that reported in van Kalmthout et al., and Yaxley et al, with sensitivity, specificity, PPV, and NPV of 0.40 (95% CI, 0.34-0.46), 0.95 (95% CI, 0.92-0.97), 0.75 (95% CI, 0.70-0.80), and 0.81 (95% CI, 0.76-0.85) and the study can be considered supportive.

Overall, none of the studies provided can be considered pivotal, but proof of diagnostic efficacy/diagnostic performance in the primary staging is based on the totality of the data. It is assumed, that the study conducted by van Kalmthout et al., has evaluated diagnostic performance of 68Ga-PSMA-11 PET most accurately, since this was a prospective study, that utilized strong SOT, adequate reading procedures and the population consisted of high-risk PCa patients in the majority (90%).

The impact of 68Ga-PSMA-11 PET (utilized for primary staging) on patient management was evaluated in 4 clinical studies Hofman et al., van Kalmthout et al., Roach et al., and Sonni et al.,). Notably, Sonni et al., is considered a flawed study, as 77% of follow-up information was collected from electronic charts and the patients themselves leading to study bias. Actual change in treatment took place in 12.6% - 43% of the cases and intended change in treatment was described in 21-28% of the cases.

Concerns have been raised on use of 68Ga-PSMA-11 PET for primary staging of PCa (Parker et al., 2020 – recommendations of European Society of Medical oncology – ESMO, Cornford P, et al.2020), as 68Ga-PSMA-11 PET in this setting has not been shown to improve clinical outcomes and the evidence is not adequate to make a recommendation concerning its use. In the recommendations from ESMO it

is stated: "Patients with localized disease on routine imaging should not be denied radical local treatment solely because metastatic lesions are identified on novel imaging techniques." Cornford P, et al. state that "the rapid introduction of PSMA PET/CT into clinical pathways without robust data that compare outcomes with standard imaging might alter the paradigm of patient management from data-driven protocols to one driven by tentative and exploratory data […]. The concern is that greater numbers of men will be subjected to life-long ADT, particularly when PSMA PET/CT is applied to a standard high-risk definition […] without evidence of a survival benefit. Authors have reported a change in management […] but although it is clear this will happen we do not have any outcome data for this new subgroup to justify these choices. […] prospective studies on survival outcomes when using PSMA PET for staging need to be conducted." These authors also recommend not to base treatment decisions on direct evidence of ^{68}Ga-PSMA-11 PET in this setting. In order to address the raised concerns, the respective information and the warning, that findings on 68Ga-Locametz PET should always be interpreted in conjunction with and be confirmed by other diagnostic methods, before subsequent change in patient management is initiated, was added in section 4.4 of the SmPC.

Notably, studies in primary staging included patients with intermediate and high-risk PCa, which high-risk patients constituting majority of the studied populations. Intermediate and high-risk PCa population are not regarded similar in terms of expected 68Ga-PSMA-11 efficacy/accuracy. No separate subgroup analysis of efficacy in the patients with intermediate-risk PCa was possible. Therefore, and also in light of the lack of data on long-term clinical outcomes, the indication was restricted to high-risk PCa patients in the primary staging setting.

Overall, the totality of the evidence presented is considered sufficient to substantiate the use of 68Ga-Locametz in the indication of primary staging in the patients with high-risk PCa with limitations of available data adequately reflected in the SmPC.

Diagnostic performance and impact on patient management - BCR

In total 5 clinical studies from literature were submitted to provide data on diagnostic performance of 68Ga-PSMA-11 PET in the patients with BCR. Impact on patient management/clinical outcome was evaluated in own clinical study (VISION) and additionally presented through data in the literature.

Key evidence of diagnostic performance of ^{68}Ga-PSMA-11-PET can be derived from Fendler et al. This was a large confirmatory study in the patients with confirmed prostate cancer and BCR. The study methodology (especially clearly defined criteria for TP and FP lesion definition) is considered acceptable. True negative cases were not defined. This is plausible at subject level analyses (as all patients would be expected to have cancer). However, at region/sub-region and lesion level analyses true negative cases could have been identified and specificity (and NPV) could have been calculated.

Efficacy analysis set excluded 46 patients "based on PET vs follow-up location mismatch (on a sub-region basis) or absence of prostate cancer both on PET and histopathologic analysis"). Scientific rationale behind and relevance of this decision is not fully clear. Bias on study outcomes cannot be excluded.

A combination of histopathologic analysis, imaging (including CT, MRI, and/or bone scan), and PSA follow-up after local/focal therapy was used (in descending priority) as the composite reference standard. This is an acceptable approach in this patient population.

The study showed good levels of diagnostic performance (PPV) at patient and region analyses as compared to histopathology (84% each) and the composite SOT (92% each). Lower bound of 95% CIs were consistently above the pre-specified value of 0.70. Thus, the primary endpoint was met.

Also, the reported sensitivities reached clinically relevant levels of 92% and 90% at patient and region levels.

Detection rate for ^{68}Ga-PSMA-11-avid lesions was 75% and showed significant relationship with PSA levels with higher detection rates observed in the patients with higher PSA. This is a common finding also with other imaging modalities.

Overall, this study was a large, well-designed and conducted positive confirmatory study in typical population with BCR. It cannot be excluded, that the patients removed from efficacy analysis might have impacted assessments of diagnostic efficacy. Therefore, there is some uncertainty around the size of the effects observed, which reached clinically relevant levels. Nonetheless, the study is regarded as supportive.

Ceci et al., conducted a mid-sized prospectively planned study in the patients with persisting PSA after RP, first time BCR without salvage therapy and BCR after salvage therapies. Acceptable composite SOT (clinical follow-up) was utilized. Overall detection rate of lesions was 53.6% (95% CI 48.1%–59.1%), which is rather low, given that all patients are considered to have cancer in the presence of PSA. On the other hand, patients displayed low levels of PSA, that could have impacted rather poor detection rates.

PET-positive patients had higher mean PSA values compared to those in PET-negative patients, which is not unexpected and is in line with other findings in the literature.

Comparison to other imaging methods (choline PET/CT, pelvic multiparametric (mp)-MRI and bone scintigraphy) showed that ^{68}Ga-PSMA-11 PET/CT was positive in 82% of cases, in which the correlative imaging also detected lesions. Whereas only 15% (22/147 cases) of the cases with positive 68Ga-PSMA PET had positive findings in other imaging. These findings suggests that 68Ga-PSMA-PET is more sensitive in detecting lesions in BCR setting than other imaging techniques. However, the detected differences were not validated, and presence of false positive cases cannot be excluded, which creates some uncertainty.

Deandreis et al. conducted an observational study with open-label reading procedures in a single centre, in a specific population of the patients with HSPC and low levels of PSA. Subgroups of patients with either persistent or recurrent PSA (BCP and BCR) were investigated. In principle, these subgroups including the low levels of PSA, were roughly similar to those presented in Ceci et al. Overall, detection (positivity) rate of lesions was also low (39.9%), with lesions mostly detected in pelvic area (23%) rather than in distant locations (extra pelvic lymph nodes, bone or visceral - 16.6%). The authors explained the low detection rates with the challenging study population composed exclusively by HSPC patients, ADT-free, presenting with low PSA levels and eligible for salvage therapy. Majority of the patients were with early recurrence and low burden of the disease (oligometastatic disease).

Most importantly, part of the PET-positive findings could be validated in this study (via histopathology in 17 cases or follow-up in 48 cases). All these cases were confirmed as true positive. These findings are regarded relevant in support of the proposed indication in the BCR setting.

Changes in the treatment were reported in 34.5% of patients overall, which suggests considerable impact.

Study by Hamed et al., reported high levels of lesion detection and sensitivity (87.8% and 98.8%) with 68Ga-PSMA-11 PET in the patients with rising PSA after definitive therapy (prostatectomy and/or radiation therapy). Interestingly, the authors also calculated specificity based on follow-up information (e.g. negative imaging after 1 year), which cannot be fully understood, as at patient level no true negative findings would be expected in this population. Therefore, specificity and accuracy values which were calculated by the authors are disregarded in this assessment.

There is a lack of clarity in regard to the chosen SOT in the Lawhn-Heath et al. and the data are difficult to interpret.

To summarize, the evidence provided by the Applicant in the indication of BCR includes one well-designed study by Fendler et al., and several exploratory studies, which all display limitations, one of them being inconsistency of diagnostic performance across the studies. Although data on diagnostic performance are variable, this may be explained with variable patient population, study designs and imaging procedures conducted. While more consistency in study outcomes would have been preferred, the data can be accepted as sufficient supportive evidence to substantiate use of 68Ga-Locametz in diagnostics of the PCa recurrence in patients with BCR.

Efficacy in PSMA-positive lesion detection – selection of patients for PSMA-targeted therapy

The Applicant claims that VISION study offers proof of clinical impact on patient outcome, as the study showed efficacy of the PSMA-based treatment (i.e., ^{177}Lu-PSMA-617) in the patients selected with 68Ga-PSMA-11 PET. This statement is not fully supported, as information regarding potential treatment of scan-negative patients was missing (as such patients were excluded). The diagnostic performance can be affected by the size of malignant lymph nodes leading to false negatives (as shown by histological examinations in primary staging), so that these patients would have missed potentially effective treatment. However, it is agreed that patients with a positive scan were good candidates for ^{177}Lu-PSMA-617 treatment, and the evidence for ^{177}Lu-PSMA-617 treatment is built upon a positive Ga-scan and Ga-PSMA-11 can be used to confirm that there is at least one lesion that would be reached by PSMA-targeted therapy.

Quantitative testing analyses that were conducted to evaluate inter-dependencies between degree of PSMA uptake and response to ^{177}Lu-PSMA-617 treatment produced partly discrepant results, which are difficult to interpret. Furthermore, the inter/intra-reader variability study has its limitations (see below).

However, data collected in the diagnostics of PCa are considered sufficient to support this indication. There is sufficient evidence showing the ability of 68Ga-PSMA-11 PET to detect PSMA-positive lesions to recommend its use for patient selection for PSMA-targeted therapy with appropriate warnings in the SmPC (section 4.4) that 68Ga-PSMA-11 PET is recommended to be used in conjunction with other diagnostic methods, including histopathology.

Notably, the targeted indication is broad and is not restricted to the compounds containing ^{177}Lu, or PSMA-11/PSMA-617 ligands. Recently published expert opinion (Fanti et al., 2022) is that PSMA PET/CT tracers are not equivalent and diagnostic efficacy cannot be extrapolated across different tracers. It is assumed, that the same applies to the tracers used for PSMA-based therapy. Since the submitted evidence is currently limited to the VISION study and ^{177}Lu-PSMA-617, this limitation has been reflected in the indication by restricting to the population similar to the one studied in VISION study. Furthermore, section 4.4 of the SmPC informs that experience of patient selection is limited to treatment with ^{177}Lu-PSMA-617.

Reviewer variability

Inter-reader and intra-reader variabilities are relevant parameters, as these suggest how reliable and reproducible assessments of the tested diagnostic tool are. For 68Ga-PSMA PET data from VISION study and those from published literature have been presented.

The study conducted by the Applicant failed to meet the primary endpoint. Moderate to high levels of inter and intra-reader agreement were observed. However, these data are questioned, and the study cannot be accepted as a supportive (even as exploratory) evidence. The reason is that the readers were asked to focus on PET-negative lesions primarily (notably, clinical reality requires detection of PET-positive lesions at first place) and detection of only one PET-positive lesion was sufficient to qualify an image as PSMA-positive. Features like number of lesions, location, size, etc., i.e., parameters relevant for e.g., monitoring of disease progression/treatment effects, were not evaluated. Detection of at least one PET-positive lesion in a patient with BCR and high levels of PSA is not regarded a challenging task, that would be sensitive enough to reliably detect differences in the reads (if such were present). Given the above, good agreement across the readers in this study is not considered of value, even as exploratory evidence.

Inter-reader variability was evaluated in a number of published studies and agreements ranged between good and almost excellent across the readers. Notably, these studies showed good level of inter-reader agreement when analysis was done by location and type of lesion. Bone metastases were detected with less inter-reader variability and visceral metastases led to lower level of agreement. Most importantly, the data were collected in primary staging and the recurrent PCa setting. Few studies specifically included images with different known pitfalls, typically leading to image misinterpretations. These data are overall encouraging and supportive for all three indications. Good agreement is suggestive of reproducibility of the image reads and reliability of the diagnostic method. Important point to be emphasised is, that the readings were performed by highly experienced specialists, who had undergone special training to read 68Ga-PSMA PET images and who partially followed pre-defined image interpretation rules/recommendations. In order to limit readers' mistakes the warning that only doctors with special training in 68Ga-PSMA-11 PET should conduct analysis of 68Ga-Locametz PET images, has been included in the SmPC section 4.4. Additionally, description of most relevant concomitant conditions/clinical situations, which may lead to misinterpretation of the images has been added in section 4.4 of the SmPC, in order to adequately inform the doctors.

2.6.7. Conclusions on the clinical efficacy

From the submitted data it can be concluded, that 68Ga-PSMA-11 PET/CT may contribute to the diagnostics of PCa during primary staging and diagnosis of PCa recurrence in patients with BCR, as well as act as a screening tool for patient selection for PSMA-targeted treatment. The initially applied indication was too broad and insufficiently substantiated by the submitted evidence, i.e. identification of PSMA positive lesions by PET in adult patients with prostate cancer. During the assessment procedure, the wording was revised based on the submitted evidence to reflect three distinct clinical settings for the indication of Locametz:

- Primary staging of patients with high-risk PCa prior to primary curative therapy,
- Suspected PCa recurrence in patients with increasing levels of serum PSA after primary curative therapy,
- Identification of patients with PSMA-positive progressive mCRPC for whom PSMA-targeted therapy is indicated.

2.6.8. Clinical safety

The primary source of safety data is Study PSMA-617-01 in which 1003 patients with mCRPC underwent a 68Ga-PSMA-11 PET/computed tomography (CT) scan. This study is the largest source of

solicited, prospectively collected safety data for the compound. The study is ongoing and the safety data for this study were presented up to a cut-off date of 27-Jan-2021.

Articles with potential supportive safety information were identified from the scientific literature database Medline up to a cut-off date of 20-Feb-2021. The largest 5 articles reporting the safety of 68Ga PSMA 11 had data in over 3000 patients and are briefly summarized.

68Ga-PSMA-11 is intended for single-use administration and long-term safety has not been specifically studied.

2.6.8.1. Patient exposure

PSMA-617-01 study (VISION):

Patients (N=1003) received a mean (standard deviation) activity injected-decay corrected dose of 167.1 (23.1) MBq and 2.0 (0.4) MBq/kg as a single i.v. injection. A dose of > 185 MBq was administered in 149 patients and was separately evaluated on safety, as this activity exceeded the recommended dose in the study.

Published studies:

More than 3000 patients with PCa received mean single doses of 150 to 227 MBq (4.05 to 6.14 mCi) (range 66-400 MBq) of 68Ga-PSMA-11 in the published studies.

Table 17*: *Overview of Study PSMA-617-01 and publications providing supportive safety data

Study/ publication	Design, population	No. of patients	Imaging acquisition and methodology	Safety assessments and timings	Mean total radiation activity
Pivotal Phase 3 study [Study PSMA-617-01] (VISION)	Designed to implement PSMA-11 as an imaging agent for PET/CT scans, centrally read, to select patients eligible for treatment with ^{177}Lu-PSMA-617	1003	At screening, patients underwent a ^{68}Ga-PSMA-11 PET/CT scan to evaluate PSMA positivity.	All TEAEs, SAEs, deaths and safety topics of interest, laboratory and vital sign abnormalities reported were recorded	167.1 MBq
Supportive publication Fendler et al (2019)	Single-arm prospective trial assessing the accuracy of ^{68}Ga-PSMA-11 PET/CT or PET/MRI scanning in patients with biochemically recurrent prostate cancer	635 (1)	PET/CT or PET/MRI was performed a mean of 64 minutes after injection of ^{68}Ga-PSMA-11 Intravenous iodinated contrast agent was administered to 613 patients (97%)	Patients were monitored for AEs during and for 2 hours after radiotracer administration. HR and BP were assessed before and after injection of radiotracer. Patients were also contacted	189 MBq (2)

Study/ publication	Design, population	No. of patients	Imaging acquisition and methodology	Safety assessments and timings	Mean total radiation activity
			Furosemide (20 mg) was administered to 588 patients (93%)	by phone to assess for the development of delayed AEs	
Supportive publication Afshar-Oromieh et al (2017)	Retrospective analysis of patients who underwent ^{68}Ga-PSMA-11 PET/CT scanning to detect recurrent prostate cancer	1007	PET/CT was performed 60 minutes after injection of ^{68}Ga-PSMA-11	Not specified [3]	227±66 MBq (range 66-400 MBq
Supportive publication Nielsen et al (2017)	Two prospective multicenter trials evaluating the safety of ^{68}Ga-PSMA-11 PET/CT scanning in patients with newly diagnosed or recurrent prostate cancer	88	10 of the 88 patients received a CE CT scan. All other patients received a low-dose CT PET/CT was performed 60±15 minutes after injection of ^{68}Ga-PSMA-11	Interview and spontaneous reporting was performed from the time of ^{68}Ga-PSMA-11 injection until the end of the day of the PET/CT BP and HR were measured at baseline, immediately post-injection, at 1, 10 and 60 minutes post-injection and upon completion of the PET/CT	166±27 MBq (range 91-223 MBq)
Supportive publication Caroli et al (2018)	Prospective trial assessing the efficacy of ^{68}Ga-PSMA-11 PET/CT scanning in patients with biochemical recurrence of prostate cancer	314	PET/CT was performed 50-60 minutes after injection of ^{68}Ga-PSMA-11	All AEs reported by the patients or recorded by healthcare personnel were recorded for safety evaluation.	150±50 MBq

Study/ publication	Design, population	No. of patients	Imaging acquisition and methodology	Safety assessments and timings	Mean total radiation activity
	after radical treatment				
Supportive publication von Eyben et al (2018)	Meta-analysis (including 12 retrospective and 3 prospective studies) evaluating the efficacy and safety of ^{68}Ga-PSMA PET/CT or PET/MRI for staging and restaging of prostate cancer	1256	PET/CT was performed a mean of the median/mean 61±13 minutes (range 45-90 minutes) after injection of ^{68}Ga-PSMA-11	Not specified [3]	172±27 MBq (range 146-236 MBq) [4]

Of note, a small proportion of patients included in the systematic review and meta-analysis by von Eyben et al 2018 may have also been included in the Afshar-Oromieh et al 2017 publication (January 2014).

[1] Note, 93% of patients received 20 mg of furosemide prior to the scan to minimize pelvic scatter artifacts.

[2] Based on a total mean dose of 5.1 mCi.

[3] Specific safety assessments and timings were not reported; however, the article states that no AEs were reported.

[4] Mean of the median/mean total radiation activity from 11 of 15 studies.

2.6.8.2. Adverse events

PSMA-617-01 study (VISION):

AEs in connection with 68Ga-PSMA-11 were collected within the timeframe of 6 days after PET procedure. To avoid interferences, patients were not to receive radiotherapy within 6 days prior to or after administration of 68Ga-PSMA-11. Other concomitant treatments were continued without a break.

Very few patients (29/1003; 2.9%) received radiotherapy within 6 days prior to or during 68Ga PSMA-11 administration and nearly half (475/1003; 47.4%) of the patients had other imaging procedures within 6 days prior to or after 68Ga-PSMA-11 administration.

Causal relationship of AEs specifically to 68Ga-PSMA-11 administration was not collected.

The most frequently reported TEAEs (in at least 0.5% patients overall) in the PSMA-11 Safety Analysis Set (6-days time-period) presented by preferred term (PT) were fatigue (1.2%), asthenia (0.9%), back pain (0.8%), nausea (0.8%), anaemia (0.7%), lymphopenia (0.6%), oedema peripheral (0.6%), constipation, decreased appetite and vomiting (0.5% each).

To enable a closer comparison of AE data from Study PSMA-617-01 with the supportive data sources, an analysis of TEAEs was performed limiting the time window to the day of or the day after 68Ga-

PSMA-11 injection. Within this shorter time window 20 patients (2.0%) had TEAEs, all events were reported in less than 0.5% of patients, were of Grade 1-2 severity except for 1 Grade 3 (fatigue) and 1 Grade 5 (SDH) event.

Table 18: ^{68}Ga-PSMA-11 Treatment-Emergent Adverse Events by Preferred Term and Maximum CTC Grade Occurring on the Day or the Day After PSMA-11 Injection (PSMA-11 Safety Analysis Set)

	Overall N=1003	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
Patients with at least one event	**20 (2.0) [34]**	**2 (0.2) [2]**
Fall	3 (0.3) [3]	0
Back pain	2 (0.2) [2]	0
Constipation	2 (0.2) [2]	0
Myalgia	2 (0.2) [2]	0
Vomiting	2 (0.2) [2]	0
Fatigue	1 (0.1) [1]	1 (0.1) [1]
Asthenia	1 (0.1) [1]	0
Dyspepsia	1 (0.1) [1]	0
Stomatitis	1 (0.1) [1]	0
Chills	1 (0.1) [1]	0
General physical health deterioration	1 (0.1) [1]	0
Injection site hematoma	1 (0.1) [1]	0
Injection site warmth	1 (0.1) [1]	0
Oedema peripheral	1 (0.1) [1]	0
Pain	1 (0.1) [1]	0
Chest injury	1 (0.1) [1]	0
Limb injury	1 (0.1) [1]	0
Scapula fracture	1 (0.1) [1]	0
Subdural haematoma	1 (0.1) [1]	1 (0.1) [1]
Weight decreased	1 (0.1) [1]	0
Musculoskeletal chest pain	1 (0.1) [1]	0
Pain in jaw	1 (0.1) [1]	0
Paraesthesia	1 (0.1) [1]	0
Claustrophobia	1 (0.1) [1]	0
Libido decreased	1 (0.1) [1]	0
Bladder spasm	1 (0.1) [1]	0
Cough	1 (0.1) [1]	0
Haematoma	1 (0.1) [1]	0

Results given as xx (xx.x) [xx] where xx=number of patients, (xx.x)=percentage, [xx]=total number of events for the patients experiencing at least one event per that row. Total number of events are based on separate records captured in the database.
Preferred terms are sorted in descending frequency, as reported in the 'Overall' column.
Every patient is counted a single time for each applicable specific adverse event with highest severity.
Coded using MedDRA version 23.1 and NCI CTCAE version 5.0.
Source: [SCS Appendix 1-Table GA-44]

Published evidence

No AEs were reported in any of the supportive safety publications with the exception of the prospective study by Fendler et al (2019), where no grade 2 or higher events were reported. Overall, 15 of 635 patients (2%) experienced grade 1 events. The most frequently reported events were diarrhea (3 patients), nausea (2 patients) and headache (2 patients). The authors made no specific causality assessments.

Table 19: AEs following ^{68}Ga-PSMA-11 imaging of prostate cancer in a prospective single-arm clinical trial (Fendler et al 2019)

System Organ Class Preferred Term	Grade 1 N=635
Any	**15 (2.4%)**
Gastrointestinal disorders	
Nausea	2 (0.3%)
Diarrhea	3 (0.5%)
Dysphagia	1 (0.2%)
Nervous system disorders	
Headache	2 (0.3%)
Dizziness	1 (0.2%)
Paresthesia	1 (0.2%)
Insomnia	1 (0.2%)
Skin and subcutaneous tissue disorders	
Rash	1 (0.2%)
General disorders and administrative site conditions	
Fatigue	1 (0.2%)
Injection site pruritus	1 (0.2%)
Cardiac and renal disorders	
Renal calculi	1 (0.2%)

Potential safety risks related to low pH

The only ADR acknowledged to be related to low pH of another diagnostic product with similarly low pH as 68Ga-Locametz is “injection site pain”.

2.6.8.3. Serious adverse event/deaths/other significant events

SAEs

Table 20: ^{68}Ga-PSMA-11 serious treatment emergent adverse events regardless of ^{68}Ga-PSMA-11 relationship by PT (Study PSMA-617-01, PSMA-11 Safety Analysis Set)

	Overall (N=1003)	
Preferred term	**All grades n (%)**	**Grade ≥3 n (%)**
Number of patients with at least one event	**16 (1.6)**	**15 (1.5)**
Spinal cord compression	2 (0.2)	2 (0.2)
Acute kidney injury	1 (0.1)	1 (0.1)
Ascites	1 (0.1)	1 (0.1)
Bicytopenia	1 (0.1)	1 (0.1)
Cardio-respiratory arrest	1 (0.1)	1 (0.1)
Gastritis	1 (0.1)	1 (0.1)
Hyponatraemia	1 (0.1)	1 (0.1)
Intracranial pressure increased	1 (0.1)	1 (0.1)
Large intestinal obstruction	1 (0.1)	1 (0.1)
Left ventricular dysfunction	1 (0.1)	1 (0.1)
Pain	1 (0.1)	1 (0.1)
Pulmonary embolism	1 (0.1)	1 (0.1)
Subdural haematoma	1 (0.1)	1 (0.1)
Tumour associated fever	1 (0.1)	0
Urinary tract infection pseudomonal	1 (0.1)	1 (0.1)

^{68}Ga-PSMA-11 Treatment-emergent adverse event (TEAE) = any AE within 6 days of ^{68}Ga-PSMA-11 dosing or any treatment related AE > 6 days from 68Ga-PSMA-11 dosing as long as prior to first dose of randomized treatment. Relatedness was not distinguished between ^{68}Ga-PSMA-11 and BSC/BSoC.
Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 23.1, NCI CTCAE version 5.0.

None of these SAEs occurred on the day or the day after ^{68}Ga-PSMA-11 injection, except for SDH. None of these SAEs were causally related to ^{68}Ga-PSMA-11.

Overall, SAEs were reported for 16 (1.6%) patients. All SAEs were reported in a single patient, except for spinal cord compression reported in 2 patients. Three SAEs (cardio-respiratory arrest, left ventricular dysfunction and subdural haemorrhage) had fatal outcomes as discussed further. None of the SAEs including the fatal events were considered to be causally related to study drug except for one event of Grade 3 hyponatremia that resolved in 5 days. According to the detailed information reported to the safety database, this SAE of hyponatremia with onset 7 days after administration of ^{68}Ga-PSMA-11 was attributed to enzalutamide and not to ^{68}Ga-PSMA-11.

Deaths

In Study PSMA-617-01, 3 deaths were reported during the treatment-emergent period (from dosing and up to 6 following days).

- A 72-year-old male presented to the emergency department (ED) after being found unresponsive two days after 68Ga-PSMA-11 administration. He died the next night following cardiopulmonary arrest. The patient was known to have had a pulmonary embolism previously and concomitant medications included warfarin, as well as antidiabetics (metformin and glipizide). The Investigator assessed the event of cardiopulmonary arrest as probably not related to ^{68}Ga-PSMA-11 or BSoC (leuprorelin).

- A 64-year-old patient was hospitalised one day after the ^{68}Ga-PSMA-11 administration, after being found unresponsive. A computed tomography (CT) scan of head showed massive right subdural hematoma (SDH) and significant subfalcine herniation. Despite intensive care treatment, he died the same day due to SDH. No head trauma was known, but the patient had reported intermittent headaches. Gosrelin had last been administered 100 days previously. Other concomitant medication included rosuvastatin for hypercholesterolemia. The Investigator assessed the SDH as definitely not related to ^{68}Ga-PSMA-11.

- A 76-year-old patient was hospitalised due to left ventricular systolic dysfunction, secondary to known coronary ischaemia and hypertension, 4 days after 68Ga-PSMA-11 administration. He was assessed as having a hypertensive crisis and pulmonary oedema, treated with unspecified beta blockers and furosemide, and discharged with a plan for further follow-up. Seven days following event onset he passed away at home. The Investigator assessed the fatal event of left ventricular dysfunction as definitely not related to ^{68}Ga-PSMA-11.

The investigator did not attribute any of these fatal events to the study. Review of the cases do not reveal any evidence that would establish causal relationship to ^{68}Ga-PSMA-11.

No deaths were reported in any of the supportive safety publications.

Other significant AEs

Designated medical events: acute kidney injury in 1 patient and bicytopenia in a second patient were reported. Both were Grade 3 events, unrelated to ^{68}Ga-PSMA-11.

Safety topics of interest: The treatment-emergent safety topics of interest for the radioactive diagnostic agent ^{68}Ga-PSMA-11 included the potential risk of hypersensitivity as well as routine safety assessments of QT prolongation and hepatotoxicity. A safety topic such as AESI is a grouping of AEs that are of scientific and medical interest, and may represent a potential concern for ^{68}Ga-PSMA-11. These groupings were defined using Medical Dictionary for Regulatory Activities (MedDRA) terms, Standard MedDRA Queries (SMQs), Higher Level Group Terms (HLGTs), Higher Level Terms (HLT) and PTs. Customized SMQs (Novartis MedDRA Query [NMQ]) were also used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. The groups defined are shown in table below.

Table 21: Safety topics of interest - MedDRA grouping definitions for analysis of Study PSMA-617-01

AE of interest	Definition
Dry mouth	Oral dryness and saliva altered (HLT)

AE of interest	Definition
Myelosuppression	Haematopoietic cytopenias (SMQ, broad)
Nausea and vomiting	Severe nausea and vomiting (NMQ, narrow)
Fatigue	Asthenic conditions (HLT)
Renal effects	Acute renal failure (SMQ, broad)
Hypersensitivity	Hypersensitivity (SMQ, narrow)
QTc prolongation	Torsade de pointes/QT prolongation (SMQ, broad)
Hepatotoxicity	Cholestasis and jaundice of hepatic origin (SMQ, broad) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ, broad) Hepatitis, non-infectious (SMQ, broad) Liver-related investigations, signs and symptoms (SMQ, broad) Liver-related coagulation and bleeding disturbances (SMQ)

Source: [Study PSMA-617-01-Listing 16.2.7.11]

The AESI groups were reported at low incidences in the following order: fatigue (2.2%), myelosuppression (1.7%), nausea and vomiting (1.3%), dry mouth (0.4%), and renal effects (0.1%).

Review of the standard safety topics of hepatotoxicity (incidence of 0.6%) and QTc prolongation (incidence of 0.1%) did not reveal concern for any relationship with ^{68}Ga-PSMA-11.

The topic of hypersensitivity was a broad MedDRA search for allergic events but also of signs and symptoms that may be suggestive of hypersensitivity. There were no ^{68}Ga-PSMA-11 AEs of hypersensitivity or anaphylactic reactions, and the retrieved event of rash was a single low-grade event that did not occur on the same day as administration of ^{68}Ga-PSMA-11, or the following day, and is unlikely to present a sign of hypersensitivity to the compound.

2.6.8.4. Laboratory findings

Laboratory values were not collected.

2.6.8.5. Safety in special populations

TEAE, Serious TEAE, Grade 3/4/5 TEAE, Drug-related TEAE, Serious drug-related TEAE, Drug-related grade 3/4/5 TEAE, and Fatal TEAE were compared in various subgroups of patients to identify possible intrinsic and extrinsic factor effects.

TEAEs were analysed with respect to subgroups of the following **intrinsic** factors:

- Age (< 65; ≥ 65-<75; ≥75 years)
- eGFR level (normal vs. mild impairment vs. moderate impairment).
- Proteinuria (≥100mg/dl, "Positive", "2+", "3+" and "4+" vs. all others).

- eGFR and proteinuria (eGFR <90 mL/min and proteinuria (≥100mg/dl "Positive", "2+","3+" and "4+") vs. (eGFR ≥90 mL/min ULN or proteinuria not in (≥100mg/dl, "Positive", "2+" and "3+", "4+")).
- Patients with renal impairment based on medical history (Yes vs No)
- Presence of liver metastases at screening (based on CRF data) (Yes vs. No), defined as at least one target and/or non-target liver lesion on or before the date of 68Ga-PSMA11 administration- and within 28 days of date of 68Ga-PSMA11 administration as captured on either the target or non-target lesion CRF pages.
- Screening liver parameters (elevated (ALT or AST >ULN) and BILI > ULN vs. non-elevated (ALT and AST ≤ULN) or BILI ≤ ULN).
- Patients with hepatic impairment based on medical history (Yes vs No)

Effect of elevated screening liver parameters and of hepatic impairment based on medical history on incidence of TEAEs could not be evaluated as there were no such patients included in the study.

Results of the remaining subgroup analyses did not suggest that any of the subgroups influenced the likelihood or severity of AEs. Exposure to ^{68}Ga-PSMA-11 was similar between patients in all the intrinsic factor subgroups with no meaningful difference between them.

Table 22: Overview of ^{68}Ga-PSMA-11 Treatment-Emergent Adverse Events by Age (PSMA-11 Safety Analysis Set)

	Overall		
	<65 years (N=251) n (%)	≥65-<75 years (N=468) n (%)	≥75 years (N=284) n (%)
TEAE	31 (12.4)	51 (10.9)	40 (14.1)
Serious TEAE	5 (2.0)	7 (1.5)	4 (1.4)
Grade 3/4/5 TEAE	9 (3.6)	7 (1.5)	5 (1.8)
Drug-related TEAE	10 (4.0)	29 (6.2)	16 (5.6)
Serious drug-related TEAE	0	1 (0.2)	0
Drug-related grade 3/4/5 TEAE	2 (0.8)	1 (0.2)	1 (0.4)
Fatal TEAE	1 (0.4)	1 (0.2)	1 (0.4)

^{68}Ga-PSMA-11 Treatment-emergent adverse event (TEAE) = any AE within 6 days of ^{68}Ga-PSMA-11 dosing or any treatment related AE > 6 days from ^{68}Ga-PSMA-11 dosing as long as prior to first dose of randomized treatment. Relatedness was not distinguished between ^{68}Ga-PSMA-11 and BSC/BSoC.

Incidence of TEAEs were analysed with respect to subgroups of the below **extrinsic** factors:

- Region (North America vs. Europe)
- Imaging procedures within 6 days prior to or after ^{68}Ga-PSMA-11 administration (Yes vs No)
- Radiotherapy within 6 days prior to or after ^{68}Ga-PSMA-11 administration (Yes vs No)
- BSC/BSoC within 6 days prior to or after ^{68}Ga-PSMA-11 administration (Yes vs No)
- NAADs within 6 days prior to or after ^{68}Ga-PSMA-11 administration (Yes vs No)
- Dose ("Dose ≤ 185 MBq ", "Dose > 185 MBq ")

Incidence of TEAEs (15.2% vs. 10.9%) and drug-related TEAEs (8% vs. 4.5%) was numerically higher in patients from Europe (N=289) compared to those in North America (N=714). Similar incidences

were reported also in the subgroups with (N=290) vs without (N=713) NAADs within 6 days to or after ^{68}Ga-PSMA-11 administration (TEAEs: 14.8% vs. 11.1% and drug-related TEAEs: 8.6% vs. 4.2%, respectively).

Large differences between the incidences of TEAEs (partly including all types of TEAEs) were reported in the subgroups with and without radiotherapy or BSC/BSoC within 6 days prior to or after ^{68}Ga-PSMA-11 administration for all types of TEAEs analysed.

Table 28: Overview of ^{68}Ga-PSMA-11 Treatment-Emergent Adverse Events by Radio- and BCS/BSoC therapy Within 6 Days Prior to or After ^{68}Ga-PSMA-11 Administration (PSMA-11 Safety Analysis Set)

	Radiotherapy		BCS/BSoC	
	Yes (N=29) n (%)	**No (N=974) n (%)**	**Yes (N=977) n (%)**	**No (N=26) n (%)**
TEAE	11 (37.9)	111 (11.4)	121 (12.4)	1 (3.8)
Serious TEAE	3 (10.3)	13 (1.3)	16 (1.6)	0
Grade 3/4/5 TEAE	4 (13.8)	17 (1.7)	21 (2.1)	0
Drug-related TEAE	5 (17.2)	50 (5.1)	55 (5.6)	0
Serious drug-related TEAE	0	1 (0.1)	1 (0.1)	0
Drug-related grade 3/4/5 TEAE	1 (3.4)	3 (0.3)	4 (0.4)	0
Fatal TEAE	1 (3.4)	2 (0.2)	3 (0.3)	0

^{68}Ga-PSMA-11 Treatment-emergent adverse event (TEAE) = any AE within 6 days of ^{68}Ga-PSMA-11 dosing or any treatment related AE > 6 days from ^{68}Ga-PSMA-11 dosing as long as prior to first dose of randomized treatment. Relatedness was not distinguished between ^{68}Ga-PSMA-11 and BSC/BSoC. Coded using MedDRA version 23.1 and NCI CTCAE version 5.0.

The incidence of TEAEs was similar in patients who received a dose ≤185 MBq (n=854) and those who received > 185 MBq (n=149) (12.9% vs. 8.1%). The incidence of SAEs, Grade 3/4/5 TEAE, and related TEAEs, was also similar between the subgroups. The single serious related TEAE, all 4 related Grade 3/4/5 TEAEs, and all three fatal TEAEs were reported in patients who received ≤185 MBq.

2.6.8.6. Immunological events

Not applicable.

2.6.8.7. Safety related to drug-drug interactions and other interactions

Not applicable.

2.6.8.8. Discontinuation due to adverse events

^{68}Ga-PSMA-11 PET/CT scan was done only once and therefore no AE leading to discontinuation was collected. However, 2 patients were not enrolled to the randomized treatments due to AEs. One had a grade 3 SAE of pain that lasted 13 days and led to initial or prolonged hospitalization. The patient recovered without sequelae, and the event was not assessed as related to study treatment. The other had a grade 3 SAE of bicytopenia that lasted 11 days and led to initial or prolonged hospitalization. The patient recovered without sequelae, and the event was not assessed as related to study treatment.

2.6.8.9. Post marketing experience

The product was recently authorized in the US (23-March-2022). No post-marketing data have been provided.

2.6.9. Discussion on clinical safety

In total, safety data on single dose of ^{68}Ga-PSMA-11 for 1003 patients with mCRPC from the clinical study PSMA-617-01 have been submitted. The actual dose administered in this study ranged from 92.8 MBq (2.5 mCi) to 287.5 MBq (7.8 mCi), with a corresponding body weight adjusted dose range of 0.9-3.7 MBq per kg (median dose: 1.9 MBq/kg) that covers the dose range proposed in the SmPC and is in line with the range utilized in majority of the published studies. Additional information from more than 3000 patients published in the literature has been also submitted. Overall, the size of tested population for assessment of safety is regarded adequate.

Data collected in the Study PSMA-617-01 (VISION) suggest that the safety profile of 68Ga-PSMA-11 is favourable. However, the provided information is seriously flawed, as systemic concomitant treatments were allowed and no placebo control was included, so that it is difficult to draw robust conclusions on safety of 68Ga-PSMA-11 from the provided information.

The incidence of TEAEs did not appear to be influenced by any of the intrinsic factors including age, race or renal impairment (normal, mild or moderate impairment as per eGFR, proteinuria, GFR and proteinuria, or renal impairment in anamnesis – yes/no), based on various subgroup analyses. Notably, the analysis did not consider ADRs of special interest (e.g., which could be assumed to be triggered by radiation exposure of healthy tissues, effects on kidneys, liver, etc.) which would have been more relevant. However, overall number of such events was very low and analysis of AEs for the subgroups at reported or preferred term level would not be meaningful.

The subgroup analyses considering extrinsic factors showed that TEAEs were more frequently reported in Europe than in US, and severe and serious AEs were somewhat more frequent in the patients without other imaging procedure within 6 days prior to or after ^{68}Ga-PSMA-11 PET. These differences were small and are not considered meaningful. In the subgroups with and without concomitant treatment with radiotherapy, NAAD or BSC/BSoC within the 6 days interval prior to, or after PET imaging, the patients with treatment had clearly higher frequency of TEAEs reported, especially in the group with radiotherapy (37.9 vs 11.4%, respectively). This finding is plausible, given that cancer treatments and especially radiotherapy are often associated with AEs.

Finally, the subgroups of patients receiving higher and lower doses of ^{68}Ga-PSMA-11 (cut-off value 185 MBq, corresponding to the dose for 84-103 kg body weight, depending on the per kg dose recommended) were compared and those with lower doses reported higher frequency of TEAEs, than those at higher doses (12.9% vs 8.1% respectively) (data not shown). This is not plausible and seems to be confounded by various interfering factors in the study, such as large observation window for AEs

(6 days prior to or after ^{68}Ga-PSMA-11 injection) combined with use of concomitant treatments and the vulnerable patient population with multiple complaints related to the background disease. To summarize, these subgroup analyses are considered confounded and less informative.

Laboratory values were not monitored in the PSMA-617-01 study. Given the micro-dose range of used 68Ga-PSMA-11, this is acceptable.

No major safety issues have been reported in supportive literature following extensive use of 68Ga-PSMA-11 (>3000 patients). One AE "Injection site pruritus" reported by Fendler et al., is considered as possibly causally related to 68Ga-PSMA-11 and was added to the product information.

Currently, the following ADRs are listed in the PI: Nausea, Constipation, Vomiting, Diarrhoea, Dry mouth, Fatigue, Injection site reactions and Chills. These are acceptable.

Given the low pH of ^{68}Ga-PSMA-11 formulation and based on clinical experience with another low-pH medicinal product (SomaKit TOC), it is expected that injection site pain may emerge after administration of 68Ga-Locametz. It is considered sufficient at this stage to include the overarching term "injection site reactions" in the SmPC to inform prescribers.

The risks related to radiation exposure for medical personnel were not addressed. However, given the relatively low/moderate dose of ^{68}Ga-PSMA-11, short physical half-life of Ga-68 and the fact, that the product will be applied by trained medical personnel, no increased radiation risks are expected compared to other nuclear diagnostics. In addition, instructions for reconstitution and radiolabeling of the product are adequately reflected in the PI. Therefore, no further risk minimisation measures are deemed necessary in this regard.

The product is not intended to be used in women. Therefore, no special requirements are foreseen for pregnancy and lactation, which is agreed.

The paediatric use is also not intended due to specificities of the disease. This is adequately reflected in the PI.

Gallium (^{68}Ga) gozetotide uptake is not specific to prostate cancer and may occur in other types of cancers, non-malignant processes and normal tissues. Detailed knowledge of the exact characteristics of gallium (^{68}Ga) gozetotide is crucial for correct interpretation of gallium (^{68}Ga) gozetotide PET images.

Considering that PET imaging interpretation errors and incorrect image interpretation still happen in clinical practice, with the level of such risk varying with experience and training of staff, educational material in the form of HCP reader training on imaging and interpretation is needed to minimise this (see RMP).

To summarize, the safety analysis in the single arm Study PSMA-617-01 is heavily confounded by concomitant use of BSC/BSoC, background disease and the lack of targeted collection of safety information. Data in the literature are difficult to interpret given the lack of control and/or detailed information that would help establish causal relationship. The to-be-marketed formulation is not compliant with the Pharmacopeia and has not yet been tested in humans. However, only a micro-dose of Locametz will be administered to the patients, PSMA-11 has no known on-target or off-target PD effects, and no major safety risks are expected with Locametz administration, and acidity of the formulation is not seen as a major safety concern, in spite of some uncertainty related to absence of clinical data with Locametz. Data collected in sizable patient population (about 4000 patients) do not raise any specific safety concerns and suggest favourable safety profile and, therefore, safety is considered sufficiently substantiated in this Application.

2.6.10. Conclusions on the clinical safety

In conclusion, a single administration of ^{68}Ga-PSMA-11 as an i.v. injection over 10-20 seconds at a dose of 3-7 mCi (111-259 MBq) is considered to have a favourable safety profile, given low number of safety reports in the literature and in VISION study and mostly mild severity of the reported AEs. Overall, the safety profile appears acceptable.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 23: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	PET imaging interpretation errors
Missing information	None

2.7.2. Pharmacovigilance plan

Table 24: On-going and planned additional pharmacovigilance activities

Study/Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
A cross-sectional knowledge and understanding survey to evaluate the effectiveness of the educational material among medical practitioners qualified to interpret PET scans (Planned)	The objectives of the proposed survey will be to evaluate: **Primary objective:** Assessment of effectiveness of Locametz educational material. **Secondary objective:** Impact of demographic data (e.g., educational background, years of clinical practice) and training factors (e.g., training method, duration of training, and user baseline training) on knowledge and diagnostic accuracy.	PET imaging interpretation errors	Submission of study protocol	30-Sep-2023

2.7.3. Risk minimisation measures

Table 25: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
PET imaging interpretation errors	**Routine risk minimization measures**: Section 4.2, 4.4. SmPC **Additional risk minimization measures:** **Educational materials for HCPs** An online or/and in-person (when online training is not accessible) image interpretation training containing the following information: • Biochemical basics • Patient administration and scanning protocol • Image reading and interpretation guidelines • PSMA PET in the context of other imaging modalities and histopathology • Interpretation of gallium (^{68}Ga) gozetotide PET scans in different use scenarios and comprehensive case study reviews (case studies with image interpretation provided by an expert and selected supplementary videos included) • Self-assessment test	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: PASS - Knowledge and understanding survey of HCPs to assess the effectiveness of the educational materials

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 23.03.2022. The new EURD list entry will

therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to SomaKit TOC. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Locametz (gozetotide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Locametz, after radiolabelling with gallium-68, 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 primary curative therapy,
- Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy,
- Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated (see section 4.4).

3.1.2. Available therapies and unmet medical need

The joint guideline on diagnosis and management of prostate cancer from European Association of Urology (EAU), European Association of Nuclear Medicine (EANM), European Society for Therapeutic Radiology and Oncology (ESTRO), European Society of Urogenital Radiology (ESUR) and International Society of Geriatric Oncology (SIOG) (Mottet et al., 2022) acknowledges poor sensitivity of the available conventional diagnostic imaging, such as CT, MRI, bone scan.

The guideline states that in the primary staging "PSMA PET/CT is more accurate for staging than CT and bone scan for high-risk disease but to date no outcome data exist to inform subsequent management" (level of evidence: 1b) and that "When using PSMA PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes." (strength rating: strong). In this setting ESMO recommends not to base clinical decision-making on the outcomes of 68Ga-PSMA PET, as impact of this diagnostic tool on clinical outcomes has not been evaluated (Parker et al., 2020).

In the BCR population, 68Ga-PSMA PET is recommended in patients after radical prostatectomy only if the results may influence subsequent therapy (strength rating: "weak") and in patients after radiotherapy if they are fit for curative salvage treatment (strength rating: "strong"). Also, choline PET/CT, fluciclovine PET/CT, multiparametric MRI (mpMRI) are being recommended depending on the specific patient population (Mottet et al.).

In relation to use of 68Ga-PSMA PET for selection of patients for PSMA-targeted therapy, as several treatments are in development (e.g. ^{177}Lu-PSMA-617)), and no similar diagnostic product has been licenced yet, an unmet medical need can be assumed.

68Ga-PSMA-11 adds value to the diagnostic landscape of PCa by detecting PSMA-positive lesions in patients with primary and recurrent PCa, as well as for targeted patient selection prior to start of a PSMA-based treatment.

3.1.3. Main clinical studies

This submission is primarily literature-based.

The [PSMA-617-01 Reviewer Variability Study] was an independent study of the Study PSMA-617-01 scans to assess the extent of inter-reader variability and intra-reader reproducibility of the ^{68}Ga-PSMA-11 PET/CT scans that were used in Study PSMA-617-01. The study is not regarded supportive due to the questionable methodology applied and as it failed primary objective. The main evidence of efficacy has been provided from:

Primary staging

- One (n=103) exploratory, prospective, 2-center, single-arm study in men with predominantly high-risk (89%), biopsy-proven PCa, with negative bone scan, who were being considered for candidates for extended pelvic lymph node dissection (van Kalmthout et al., 2020). The trial aimed to investigate diagnostic performance of PSMA PET-CT in detection of pelvic LN metastases.
- One large (n=277) exploratory, prospective, 2-center, single-arm, Phase 3 study in men with intermediate and high-risk PCa, who were considered for prostatectomy (Hope et al., 2021). Aim of the study was to assess diagnostic accuracy of 68Ga-PSMA-11 PET for the detection of pelvic nodal metastases.

BCR

One large (n=316) confirmatory, prospective, multicenter, single-arm study, designed to assess the accuracy of 68Ga-PSMA-11 PET imaging in localizing recurrent PC (Fendler et al., 2019). Patients with biopsy-confirmed prostate cancer after radical surgical treatment and/or radiation therapy (RT) with increased levels of PSA (0.2 ng/mL or greater measured during 6-13 weeks post-surgery, or Nadir equal or greater than 2 ng/mL after RT). The key endpoint used to evaluate accuracy was the PPV of 68Ga-PSMA-11 PET on a per-patient and per region basis. Lesions were validated by histopathologic analysis (primary endpoint) and a composite reference standard (secondary endpoint).

Patient selection for PSMA-targeted therapy

^{68}Ga-PSMA-11 was used for patient selection in the Applicant's clinical VISION study (Study PSMA-617-01). However, these data are of very limited relevance as the setting of VISION covers only a small part of the proposed indication, no data are provided about the fate of scan-negative subjects, validation of 68Ga-PSMA-11 findings by means of SOT/surrogate SOT was not done, comparative analysis to other imaging options has not been conducted, no AE reporting focused on assessment of 68Ga-PSMA-11 safety was performed and the Applicant's own product was not used in the trial.

3.2. Favourable effects

The mode of action is considered established. PSMA is expressed in more than 90% of primary tumours when imaging occurs before initial therapy.

Key evidence of favourable effects of 68Ga-PSMA-11 has been investigated in two settings which are part of the proposed indication: primary staging and diagnosis of PCa recurrence in BCR.

- Good diagnostic performance was observed in the main studies:

Primary imaging:

Positron emission tomography patient-based sensitivity of 41.5% (95% CI 26.7-57.8), specificity of 90.9% (95% CI 79.3-96.6), and positive and negative predictive values of 77.3% (95%CI 54.2-91.3) and 67.6% (95% CI 55.6-77.7), respectively, for detecting LN metastases (van Kalmthout et al.).

Patient based sensitivity, specificity, positive predictive value, and negative predictive value for pelvic nodal metastases were 0.40 (95%CI, 0.34-0.46), 0.95 (95%CI, 0.92-0.97), 0.75 (95%CI, 0.70-0.80), and 0.81 (95%CI, 0.76-0.85), respectively (Hope et al.).

BCR:

On a per-patient basis, the PPV was 0.84 (95% CI: 0.75-0.90) by histopathologic validation (n = 87) and 0.92 (95% CI: 0.88-0.95) by the composite reference standard (n = 217). On a per-region basis, the PPV was 0.84 (95% CI, 0.76-0.91) by histopathologic validation (n = 90) and 0.92 (95% CI, 0.88-0.95) by the composite reference standard (n = 249). Sensitivity by histopathologic validation was 0.92 (95% CI, 0.84-0.96) on a per-patient basis, and 0.90 (95% CI, 0.82-0.95) on a per-region basis.

- Relevant impact on patient management was reported:

Primary imaging:

Impact on patient management ranged from 12.6% to 43%.

BCR:

Impact on patient management ranged from 28.6% to 78%.

- *Moderate/good/very good agreement in image reads.*

3.3. Uncertainties and limitations about favourable effects

- ^{68}Ga-PSMA-11 is dosed based on bodyweight. Supportive evidence (dose-finding studies) for this body-weight based dosing was not provided. However, there is large evidence available of effective use of the substance in the recommended dose.
- Impact of ^{68}Ga-PSMA-11 on clinical outcome in the setting of primary staging is unknown. However, lack of this information is reflected in the SmPC section 4.4.
- Evidence of use for patient selection for treatment with PSMA-based therapy is limited to data from VISION study, including the specific and narrowly defined patient population, and treatment with ^{177}Lu-PSMA-617. Respective information has been added in the SmPC section 4.4 to inform the doctors accordingly.

3.4. Unfavourable effects

Nausea, constipation, vomiting, diarrhoea, dry mouth, fatigue, injection site reactions (injection site haematoma, injection site warmth and injection site pruritus) and chills are considered as ADRs of ^{68}Ga-PSMA-11. Injection site pain may also occur given the low pH of the to-be-administered solution.

In the study conducted by the Applicant 12.2% of patients had AEs in the defined treatment-emergent period in the days following ^{68}Ga-PSMA-11 administration. The most frequent event was fatigue (1.2%), all other events were reported in less than 1.0% of patients. 1.6% of patients had at least one SAE, 2.1% had AEs of grade $\geq$ 3 in severity and 5.5% AEs considered as drug-related by the investigator. None of the SAEs or deaths was considered causally related to ^{68}Ga-PSMA-11. The incidence of AEs in Study PSMA-617-01 was higher compared to the supportive literature.

Few additional AEs were reported in the literature describing more than 3000 patients.

3.5. Uncertainties and limitations about unfavourable effects

- In the VISION study methodology of AE collection was flawed and use of concomitant systemic treatment was allowed, so that assessment of causal relationship is difficult. However, additional safety data from the literature do not suggest any specific and worrisome safety risks.
- Commercial formulation of gozetotide has not yet been tested in humans and it is unclear what will be its tolerability, also given the lower pH specification, than foreseen by the Pharmacopeia monograph "Gallium (^{68}Ga) PSMA-11 Injection" (Eur. Ph. 3044). However, this is not expected to lead to critical safety findings based on clinical experience with another product with similarly low pH. Also, a warning about potential tolerability issues has been added in the product information (SmPC section 4.4).
- Safety in patients with severe renal impairment has not been studied. Absence of these data is adequately reflected in the product information.

3.6. Effects Table

Table 26: Effects Table for 68Ga-gozatotide "for the identification of prostate specific membrane antigen (PSMA) positive lesions by positron emission tomography (PET) in adult patients with prostate cancer" (data cut-off 27.01.2021 for VISION; 20.02.2021 for published evidence):

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Accuracy	Clinical setting: **Primary staging** (patient level); Comparator: CT and bone scan combined; Validation against histology or composite SOT	% (95% CI)	92% (88-95%)	65% (60-69%) P<0.0001	Validity of some of the soft criteria is questioned; unclear how many patients were diagnosed with use of these criteria; level of bias not assessable. Weak evidence.	Hofman et al. 2020
Sensitivity			85% (74-96%)	38% (24-52%)		
Specificity			98% (95-100%)	91% (85-97%)		
Equivocal results			7% (4-13%)	23% (17-31%) p<0.001		
Sensitivity	Clinical setting: **Primary staging** (patient level); Validation against histology SOT	% (95% CI)	41.5% (26.7-57.8)	NA	Strong SOT (Histopathology), prospective study, appropriate blinding and reading procedure. Small exploratory study. Moderately strong evidence.	Van Kalmthout et al. 2020
Specificity			90.9% (79.3-96.6)			
PPV			77.3% (54.2-91.3)			
NPV			67.6% (55.6-77.7)			
PPV	Clinical setting: **BCR diagnosis** (patient level); Comparator: NA; Validation against histology or composite SOT	% (95% CI)	Against SOT: 84% (75-90%) Comp SOT: 92% (88-95%)	NA	46 patients removed from efficacy analysis. Therefore, the analyses may be biased. Strong evidence	Fendler et al. 2019
Sensitivity			Against SOT: 92% (84-96%)			

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Detection rate	Proportion of patients with positive PET (no validation)	%	75%			
Sensitivity	Clinical setting: **Primary staging** (patient level); Validation against histology	% (95% CI)	40% (34-46%)	NA	Strong SOT (Histopathology), prospective study, appropriate blinding and reading procedure. Large confirmatory study. Failed primary endpoint. Moderately strong evidence.	Hope et al. 2021
Specificity			95% (92-97%)			
PPV			75% (70-80%)			
NPV			81% (76-85%)			
Unfavourable Effects						
TEAEs	AEs reported within 6 days after 68Ga-PSMA-11 injection.	% (n/N)	12.2% (122/1003)	NA	AE collection was not done specifically for 68Ga-PSMA-11; data on causal relationship are not reliable. Data confounded by background disease and concomitant treatment.	Study PSMA-617-01 (VISION)
SAEs			1.6% (16/1003)			
Death			0.3% (3/1003)			
Fatigue			1.2% (12/1003)			
Effective radiation dose	NA	mSv	3.30-5.70	NA	Comparable to a pelvic CT-scan (7.3 mSv)	Sandgren et al., 2019
Abbreviations: BCR, Biochemical recurrence. CI, confidence interval. PPV Positive predictive value. AE, adverse event.						

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Generally, poor sensitivity and low accuracy are acknowledged as weaknesses of currently used conventional imaging (e.g., CT, MRI, bone scan) and it is recognised that availability of more sensitive non-invasive diagnostic tool would be important to guide the doctors in decision-making on treatment/patient management in PCa. Submitted data suggest, that ^{68}Ga-PSMA-11 PET/CT may offer improvements in diagnostics of PCa during primary staging and diagnosis of PCa recurrence in patients with BCR, as well as a screening tool for patient selection for PSMA-targeted treatment.

The assessment of impact of patient management showed considerable effects and moderate to high levels of inter-reader agreement are suggestive of reliability of the image read.

These are all relevant effects, which could translate into clinical benefit, if sufficient risk-minimisation measures are put in place, if the target populations are correctly defined and if the SmPC includes adequate warnings in order to inform health care professionals. All these conditions are met by the current version of the SmPC.

No critical findings (risks/unfavourable effects) were detected in relation with ^{68}Ga-PSMA-11. Overall, safety profile of the product appears acceptable. There is a remaining uncertainty regarding the local

tolerability of the to-be-marketed formulation, that has not been tested in humans yet. However, this uncertainty is not relevant enough to negatively impact the safety profile. Safety will be monitored post marketing with routine pharmacovigilance activities.

3.7.2. Balance of benefits and risks

^{68}Ga-PSMA-11 PET/CT may contribute to the diagnostics of PCa during primary staging and diagnosis of PCa recurrence in patients with BCR, as well as act as a screening tool for patient selection for PSMA-targeted treatment. Given the low number of safety reports in the literature and in the VISION study and mostly mild severity of the reported AEs, it can be concluded that the benefits outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Locametz is positive, subject to the conditions stated in section 'Recommendations'.

Divergent position is appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Locametz is favourable in the following indication(s):

Locametz, after radiolabelling with gallium-68, 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 primary curative therapy,
- Suspected PCa recurrence in patients with increasing levels of serum prostate specific-antigen (PSA) after primary curative therapy,
- Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated (see section 4.4).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Locametz in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The educational programme is aimed to reduce the risk of PET imaging interpretation errors.

The MAH shall ensure that, in each Member State where Locametz is marketed, medical practitioners qualified to interpret PET scans in their country who are expected to use gallium (^{68}Ga) gozetotide have access to the self-training educational material.

The Locametz educational material for HCPs [gallium (^{68}Ga) gozetotide imaging interpretation training] contains the following key elements:

- Introduction to gallium (^{68}Ga) gozetotide
- Biochemical basics
  - Chemical structure
  - PSMA
  - Mechanism of uptake
- Patient administration and scanning protocol
  - Patient preparation
  - Injection recommendation
  - Scanning protocol
- Image reading and interpretation guidelines
  - Locametz special warnings and precautions for use
  - Guidelines and practical tips
  - PSMA visual assessment scoring scale
- PSMA PET in the context of other imaging modalities and histopathology
- Interpretation of gallium (^{68}Ga) gozetotide PET scans in different use scenarios and comprehensive case study reviews (case studies with image interpretation provided by an expert and selected supplementary videos included)
  - Physiological distribution of gallium (^{68}Ga) gozetotide
  - Primary staging of patients with high-risk PCa prior to primary curative therapy

    - Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy (including cases with and without prior injection of furosemide)
    - Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA targeted therapy is indicated
    - Rare locations
    - PSMA expression in other malignant tumours
    - Pitfalls
- Self-assessment test

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that gozetotide is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Divergent position

Divergent position to the majority recommendation is appended to this report.

APPENDIX

DIVERGENT POSITION DATED 13 October 2022

DIVERGENT POSITION DATED 13 October 2022

Locametz EMEA/H/C/005488/0000

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Locametz indicated for:

Locametz, after radiolabelling with gallium 68, 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 primary curative therapy,
- Suspected PCa recurrence in patients with increasing levels of serum prostate specific antigen (PSA) after primary curative therapy,
- Identification of patients with PSMA positive progressive metastatic castration resistant prostate cancer (mCRPC) for whom PSMA targeted therapy is indicated.

The reason for divergent opinion was the following:

The reasons for divergent opinion are based on the insufficient demonstration of the efficacy and safety profile of Locametz. Indeed, Locametz was not even used in the Applicant's clinical VISION study (Study PSMA-617-01).

In summary, the final to-be-marketed product under the MAA has not been tested in humans and no dedicated bridging study has been conducted, based on the rationale that no bioequivalence studies are required for water-soluble i.v. formulations containing the same active substance in accordance with the EMA guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

As a conclusion, we are of the opinion the benefit/risk ratio cannot be determined for Locametz after radiolabelling with gallium-68 for the detection of prostate-specific membrane antigen (PSMA)-positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa).

Alexandre Moreau