EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/237809/2017
Committee for Medicinal Products for Human Use (CHMP), Corr. 1 [1]

Assessment report

Axumin

International non-proprietary name: fluciclovine (18f)

Procedure No. EMEA/H/C/004197/0000

Note

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

[1] 5 June 2019 - Title of the false positives and true negatives has been switched between false positives and true negatives.

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List of abbreviations

AATs	Amino acid transporters
BCR	Biochemically recurrent
BED	Blue Earth Diagnostics Ltd
BIE	Blinded image evaluation
BPH	Benign prostatic hypertrophy
Boc	Tert-butylyoxycarbonyl
CI	Confidence interval
CT	Computerized tomography
CTD	Common technical document
DR	Detection rate
eCRF	Electronic case report form
ECG	Electrocardiogram
EOS	End of synthesis
FDG	Fludeoxyglucose
GCP	Good clinical practice
GEHC	GE Healthcare
GI	Gastrointestinal
hERG	Human Ether-à-go-go-Related Gene
HV	Healthy volunteers
IV	Intravenous
LN	Lymph node
MRI	Magnetic resonance imaging
NMP	Nihon Medi-Physics
NOEL	No observed effect level
NPV	Negative predictive value
OHACBC	*anti*-1-amino-3-hydroxycyclobutane-carboxylic-acid
OPTT	Orthotopic prostate tumour transplantation
OUS	Oslo University
PCa	Prostate cancer
PET	Positron Emission Tomography
PET-CT	Positron emission tomography - computerized tomography
Ph. Eur.	European Pharmacopeia
pi	Post-injection
PPV	Positive predictive value
PSA	Prostate specific antigen
PSA-DT	Prostate specific antigen doubling time
RCP	Radiochemical purity
SPECT	Single photon emission computerized tomography
SUV	Standardized uptake values
TEAE	Treatment emergent adverse event
TRUS	Transrectal ultrasound

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Blue Earth Diagnostics Ltd submitted on 4 December 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Axumin, 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 26 March 2015.

The applicant applied for the following indication: *"Axumin is a radioactive diagnostic agent for PET imaging of adult men with suspected prostate cancer recurrence. Axumin PET imaging may identify sites of prostate cancer recurrence. Suspected prostate cancer recurrence is based upon elevated blood prostate specific antigen (PSA) levels following initial therapy".*

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that fluciclovine (^{18}F) was considered to be a new active substance.

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 tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0256/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001644-PIP02-14 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

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.

New active Substance status

The applicant requested the active substance fluciclovine (^{18}F) 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.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Harald Enzmann Co-Rapporteur: Concepcion Prieto Yerro

- The application was received by the EMA on 4 December 2015.
- The procedure started on 31 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 22 March 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 23 March 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 01 April 2016.
- During the meeting on 28 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 03 May 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 October 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 November 2016.
- During the PRAC meeting on 01 December 2016 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 06 December 2016.
- During the CHMP meeting on 15 December 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 February 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 17 March 2017.
- During the meeting on 23 March 2017, 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 Axumin on 23 March 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The prostate is located in the pelvis between the bladder and the external urinary sphincter. There are three distinct zonal boundaries (the central zone, the transition zone and the peripheral zone) in the prostate gland of an adult male. In older men, the transition zone that surrounds the uretha can enlarge from non-malignant growth called benign prostatic hyperplasia (BPH), which affects both the epithelial and the mesenchymal cells

of the prostate. However most of the cancers in the prostate originate in the peripheral zone. Prostate cancer is generally multifocal and present through out the gland. The spread of the disease may occur initially through the capsule where the ejaculatory ducts enter the prostate or in the region of the bladder neck and can progress to the seminal vesicles or the bladder to invade the surrounding tissues and muscles. There is no causal relationship between prostate cancer and BPH.

Patients with prostate cancer will have received treatment based on the staging, grade and the extent of the disease at baseline. Primary curative procedures such as radical prostatectomy, radiotherapy or cryotherapy are well-established therapeutic options in the management of localised prostate cancer. Despite technical improvements, there is still a significant risk of cancer recurrence after primary curative therapy.

2.1.2. Epidemiology

Prostate cancer is the most common malignancy in men (> 70 years of age) in Europe, with an estimated 417,000 new cases in 2012. It is a major health concern, especially in developed countries with their greater proportion of elderly men in the general population. There is considerable variability in the incidence reported in individual member states, with a 7-fold (25 to 193 per 100,000) difference across the EU. The highest rates of prostate cancer are seen in Northern and Western Europe and the lowest rates in Central and Eastern Europe[2]. The relative survival statistics for men with prostate cancer are generally good, with an overall 5-year relative survival for 2005-2007 in the EU estimated at 81.7%[3]. Localized disease confined to the prostate is usually not lethal, and may display an indolent course, but metastatic prostate cancer can be aggressive and deadly, accounting for nearly all prostate cancer-related deaths. Approximately 92,000 men died of prostate cancer in the EU in 2012, the third most common cause of cancer death in men. Up to one third of patients treated with curative procedures of the localised primary prostate cancer will experience recurrent disease within 10-15 years following primary treatment[4,5,6] .

2.1.3. Biologic features

The vast majority of prostate cancers are arising from adenocarcinomas. The degree of differentiation has prognostic value and is graded using the Gleason grading system. The scale measures the patterns of growth from 1-5 and the differentiation of cells from well to poorly differentiated.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Prostate cancer is staged using the TNM (tumour, node, and metastasis) staging system from the American Joint Committee on Cancer /International Union Against Cancer. The classification designates the primary tumour, regional lymph nodes, and distant metastases. T1 stages comprise cancers that are not palpable and have been identified using histology or by other means such as rises in PSA levels, T2 to T4 categories may

[2] Ferlay J., Steliarova-Foucher E., Lortet-Tieulent J., Rosso S., Coebergh J.W., Comber H., et al: Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013; 49: 1374-1403.
[3] Trama A, Foschi R, Larranaga N, Sant M, Fuentes-Raspall R, Serraino D, Tavilla A, Van Eycken L, Nicolai N and the EUROCARE-5 Working Group. Survival of male genital cancers (prostate, testis and penis) in Europe 1999–2007: Results from the EUROCARE-5 study. European Journal of Cancer 2015; 51: 2206 - 2216
[4] Freedland SJ and Moul JW. Prostate Specific Antigen recurrence after definitive therapy. J Urol, 2007. 177, 1985-1991
[5] Simmons MN, Stephenson AJ, Klein EA. Natural history of biochemical recurrence after radical prostatectomy: Risk assessment for secondary therapy. European Urology, 2007; 51: 1175–1184.
[6] Agarwal PK, Sadetsky N, Konety BR, Resnick MI, Carroll PR et al. Treatment Failure After Primary and Salvage Therapy for Prostate Cancer. Likelihood, Patterns of Care, and Outcomes. Cancer 2008;112:307–14.

not be palpable but are visible during imaging, such as transrectal ultrasound (TRU) or magnetic imaging resonance (MRI).

The value of the presence/increase levels of prostate-specific antigen (PSA) in the serum is used as a marker to indicate the possible presence of prostate cancer. Measurement of PSA is a cornerstone in follow-up after local treatment of the primary tumour. Local recurrence after curative treatment is possible without a concomitant rise in PSA level and has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. PSA measurement and digital rectal examination comprise the most useful combination for first-line examination in follow-up after radiotherapy or radical prostatectomy, but PSA measurement may be the only test in cases with favourable pathology (< pT3, pN0, Gleason < 8).

The PSA level that defines treatment failure differs between men who have undergone radical prostatectomy and those who have received radiotherapy. However, following radical prostatectomy, there is international consensus that recurrent cancer may be defined by two consecutive PSA values of > 0.2 ng/mL and rising (Moul 2000). After primary radiotherapy, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure is any PSA increase >2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir .

2.1.5. Management

Despite therapeutic improvements, between 27% and 53% of all patients undergoing radical prostatectomy or radiotherapy will develop PSA-recurrence. A rising PSA level usually precedes metastatic progression and this is defined in current clinical guidelines as biochemically recurrent prostate cancer (BCR)[7,8]. Determining the location of the recurrence is critical, as this defines the stage and prognosis of the disease as well as the optimal choice of therapy.

Imaging techniques such as MRI, US and CT have been considered to provide minimal clinical utility in screening, early detection or diagnosis of prostate cancer. However, imaging does have role in determining the location of metastases and the extent of the recurrence. The diagnostic accuracy of standard imaging tests for the identification of sites of recurrence is low. Almost 90% of the standard battery of imaging tests, may be negative. Bone metastases, one of the most frequent location of metastases from prostate cancer, are generally detected using technetium (^{99m}Tc) ddiphosphonates with not infrequent false-positive cases and by sodium fluoride (^{18}F). Excluding recurrences is also of paramount importance in the diagnostic work-up of suspected recurrent prostate cancer.

Fluciclovine (^{18}F) is proposed for detection of recurrences of prostate cancer in any location (both regional and distant sites). Some other radiopharmaceuticals have been used in the diagnostic work-up of prostate cancer with different indications and limitations:

- Prostascint (capromab pendetide), approved in the US for overall detection recurrences (both local and distant), has yielded disappointing results according to the 2015 EUA guideline on prostate cancer.
- Choline PET-CT radiopharmaceuticals, which visualize the choline metabolism associated with the tumour cells, are being used in the EU for detection of recurrences of prostate cancer in any

[7] Roach M, Hanks G, Thames H, Jr, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006; 65:965–974.
[8] Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, Klein E, Michalski J, Roach M, Sartor O, Wolf JS Jr, Faraday MM. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol. 2013 Aug;190(2):441-9

location (both local, regional and distant). Three radiopharmaceuticals are used: choline (^{11}C), fluoromethylcholine (^{18}F) and fluoroethylcoline (^{18}F). Choline (^{11}C) is neither registered in Europe, and to our data, nor validated. Fluoroethylcholine (^{18}F) (DE/H/4293/01/MR) is registered in the EU for N staging of metastatic lymph nodes in patients at risk for metastases and fluoromethylcholine (^{18}F) (authorized in FR) with varying indications for the detection of (local, regional and distant) recurrences depending on the particular commercial product. The choline PET results are, however, hampered by the fact that other pathologies involving inflammation like benign prostatic hyperplasia, chronic prostatitis or high grade prostatic intraepithelial hyperplasia also accumulate choline and can confound the results.

- Acetate (^{11}C) is neither validated for the diagnostic work-up of prostate cancer nor registered in the EU.
- For detection of bone lesions, labelled diphosphonates for bone scan and sodium fluoride (^{18}F) are approved in the EU. Bone scan has been the most widely used method for evaluating bone metastases of prostate cancer. Sodium fluoride (^{18}F) show superior sensitivity to bone scanning but both are limited by a relatively low specificity (2015 EAU guideline on prostate cancer) and by the fact that they do not assess local nor extraosseous recurrence.

Diagnostic performance of the imaging tests used in the work-up of prostate cancer varies depending on different clinical factors, particularly the PSA values.

It is thought that PET radiopharmaceuticals that visualize the increased amino acid transport associated with tumour cells could be an alternative for use in prostate cancer imaging. Fluciclovine (^{18}F) is such a PET radiopharmaceutical.

About the product

Fluciclovine (^{18}F) is the International Non-proprietary Name (INN) for the active substance *anti*-1-amino-3-fluorocyclobutane-1-carboxylic acid, labelled with fluorine (^{18}F). Fluciclovine (^{18}F) is a synthetic amino acid which is transported across mammalian cell membranes by amino acid transporters such as LAT-1 and ASCT2. The activities of LAT-1 and ASCT2 are known to be upregulated in prostate cancer, providing a mechanism for the enhanced accumulation of fluciclovine (^{18}F) in prostate cancer.

As an amino acid analogue, this agent is preferentially accumulated by prostate tumour cells due to their increased metabolic needs; however, unlike naturally occuring amino acids, this non-natural amino acid-analogue radiopharmaceutical is not metabolized. Accordingly, fluciclovine (^{18}F) accumulates in prostate tumour cells and can potentially be used to image tumours using PET. There is slow excretion to the bladder, therefore the visualization of the pelvis region is not obscured by bladder uptake.

The included nuclide fluorine (^{18}F) has a longer radioactive half-life (110 min) than carbon (^{11}C) and shipping of a radiopharmaceutical labelled with fluorine (^{18}F) is both possible and practical as demonstrated with the well established tracer fludeoxyglucose (^{18}F), making fluciclovine (^{18}F) PET imaging potentially available to imaging centres all across the EU.

Pharmacotherapeutic group: Other diagnostic radiopharmaceuticals for tumour detection, ATC code: V09IX12.

The following indication was proposed by the applicant:

This medicinal product is for diagnostic use only.

Axumin is a radioactive diagnostic agent for positron emission tomography (PET) imaging of adult men with suspected prostate cancer recurrence. Axumin PET imaging may identify sites of prostate cancer recurrence. Suspected prostate cancer recurrence is based upon elevated blood prostate specific antigen (PSA) levels following initial therapy.

The proposed activity is 370 MBq to be administered by slow intravenous injection.

The following indication was agreed by the CHMP:

"This medicinal product is for diagnostic use only.

Axumin is indicated for Positron Emission Tomography (PET) imaging to detect recurrence of prostate cancer in adult men with a suspected recurrence based on elevated blood prostate specific antigen (PSA) levels after primary curative treatment.

For the limitations in the interpretation of a positive scan, see section 4.4 and 5.1."

A PET scan with fluciclovine (^{18}F) should be administered by appropriately qualified healthcare professionals.

Images should only be interpreted by readers trained in the interpretation of PET images with fluciclovine (^{18}F).

Posology
Adults
The recommended activity for an adult is 370 MBq fluciclovine (^{18}F).

Type of Application and aspects on development

This is a full application in accordance with article 8(3) of Directive 200l/83/EC as amended, for approval of a new active substance through the centralised procedure (according to Regulation (EC) No 726/2004).

This radiopharmaceutical has been recently approved in the USA on May 2016.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection containing 1,600 MBq/mL and 3,200 MBq/mL at the date and time of calibration of fluciclovine (^{18}F) as active substance.

Other ingredients are: sodium citrate, hydrochloric acid, sodium hydroxide, and water for injections.

The product is available in a multidose glass vial of capacity 10 ml sealed with a rubber closure and aluminium overseal as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance in Axumin is fluciclovine (^{18}F), a small chemical molecule labelled with fluorine-18, a positron emitting radionuclide with a half-life around 110 minutes.

As with most of the PET radiopharmaceuticals containing ^{18}F, due to the short physical half-life of the radionuclide, the radiolabelled active substance cannot be isolated as it is synthesized *in situ* during the manufacture of the finished product. This manufacturing process is a continuous, highly automated process that uses ^{18}F fluoride and a non-radioactive chemical precursor as the key starting material. In this application the chemical precursor for the synthesis of fluciclovine (^{18}F) is called AH113487.

The guideline on radiopharmaceuticals states that the chemical precursor should satisfy the requirements of the guideline Note for Guidance on Summary of Requirements for Active Substances in Part II of the Dossier (CHMP/QWP/297/97 Rev.1). Accordingly, the application includes complete information for the chemical precursor AH113487 as well additional complete information for the non-isolated (radiolabelled) active substance fluciclovine (^{18}F).

Chemical precursor AH113487

General information

The chemical name of AH113487 is ethyl cis-1-(N-tert-butoxycarbonyl) amino-3-[(trifluoromethyl)-sulfonyloxy] cyclobutanecarboxylate corresponding to the molecular formula $C_{13}H_{20}F_3NO_7S$ and has a relative molecular mass 391.36 g/mol and has the following structure:

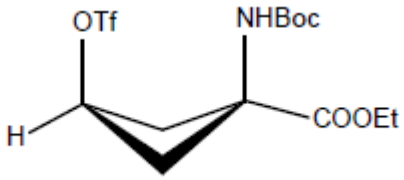


Figure 1: Structure of chemical precursor AH113487

The chemical structure of the precursor AH113487 has been adequately demonstrated by elemental analysis, mass spectroscopy, infrared spectroscopy (IR), ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, and X-ray crystallography.

AH113487 is a white to off-white powder soluble in acetonitrile, chloroform and dichloromethane; sparingly soluble in cyclohexane and slightly soluble in pentane and hexane. It is not hygroscopic.

The molecule can exist, in theory, in two isomer forms – *syn* or *anti*. The manufacturing process leads to the *syn* form.

Manufacture, characterisation and process controls

AH113487 is synthesized in six main steps using well defined starting materials with acceptable specifications.

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

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

The precursor is packaged in an amber glass Duran bottle with a teflon line screw cap. The glass conforms to Ph. Eur. Type 1. Appropriate testing has been performed to demonstrate that the container is suitable to store AH113487 for the duration of the retest period.

Specification

The precursor specification includes tests for appearance, identification (IR), assay (HPLC), residual solvents (GC), residual water (KF), palladium (ICP-OES), related substances (^{1}H NMR, ^{19}F NMR) and microbial enumeration test (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.

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 has been presented.

Batch analysis data from 7 commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 3 batches of the precursor from the proposed manufacturer stored in Type 1 glass vials with a FluroTec coated stopper, which are similar to the Type 1 glass bottle with teflon lined cap used for bulk storage of the precursor. Samples of two batches were stored for 11.5 and 36 months respectively under long term conditions at -20 °C/ambient humidity, for 11.5 and 24 months respectively under accelerated conditions at 5 °C/ambient humidity, and for up 3 and 6 months under stress conditions at 25 °C/60% RH. One batch was stored for 24 months accelerated conditions at 5 °C/ambient humidity, and for up 6 months under stress conditions at 25 °C/60% RH according to the ICH Guideline. Photostability testing following the ICH guideline Q1B was performed on one batch.

A study to determine the effect of exposure to moderate humidity has also been carried out. Samples of one batch were prepared in glass vials. Vials without caps were placed in a stability room at 25 °C and 60% relative humidity so that the powder was directly exposed to the environment. In order to be able to differentiate between the effects of temperature and moisture, control samples were prepared in capped vials and the vials were placed in a desiccator in the stability room. Samples were removed for analysis after 1, 3 and 7 days storage.

The following parameters were tested*:* appearance, assay, related substances, and residual water. The analytical methods used were the same as for release and were stability indicating.

The results demonstrated that the precursor manufactured by the proposed supplier is sufficiently stable at the recommended storage temperature.

Although no significant effect from exposure of material to light has been observed, the long term storage condition will include protection from light as this is accepted good practice.

Although, the precursor is not hygroscopic, prolonged exposure to a humid atmosphere does lead to an increase in the rate of degradation with trifluoromethanesulfonic acid being the main impurity formed. The container closure system used for normal storage is adequate to control this degradation process.

Overall the stability results justify the proposed retest period of 24 months stored at 5 °C/ambient humidity and protected from light in the proposed container.

Fluciclovine (^{18}F)

General information

The chemical name of fluciclovine (^{18}F) is anti-1-amino-3-[^{18}F] fluorocyclobutane-1-carboxylic acid corresponding to the molecular formula $C_5H_8{}^{18}FNO_2$ and has a relative molecular mass 132.13 g/mol and has the following structure:

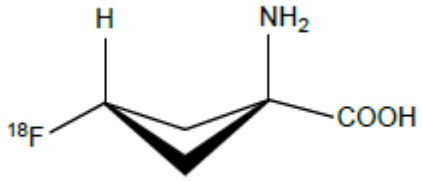


Figure 2: Structure of active substance fluciclovine (^{18}F)

The chemical structure of the active substance has been adequately demonstrated by infrared spectroscopy (IR), elemental analysis, ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, mass spectroscopy, and X-ray crystallography.

Fuciclovine (^{18}F) is a white powder soluble in tetrahydrofuran, acetone, acetic acid, ethyl acetate and pyridine and slightly soluble in chloroform, ethanol, water, acetonitrile, methanol, triethyl amine. It is not hygroscopic.

Fluciclovine is not chiral but does exist in two geometrical forms: the anti-form, where the fluorine atom is on the opposite site of the cyclobutane ring to the amino group, and the syn form where they are on the same side of the ring. The clinical relevant active substance is the anti-isomer. Presence of *syn* isomer is minimised in the production process of the chemical precursor. The synthesis of the anti-isomer is assured by the use of nearly pure syn-isomer of the cold precursor, which switches as a result of the Walden-inversion in the case of the nucleophilic substitution into the desired radiolabelled anti-isomer.

Polymorphism has not been observed for the active substance.

Manufacture, characterisation and process controls

The active substance fluciclovine (^{18}F) is prepared from the precursor AH113487 by nucleophilic substitution of a triflate group by ^{18}F-fluoride, followed by two deprotection steps. Due to the short half-life of the ^{18}F-fluorine radioisotope, each batch is prepared on the day of clinical use.

The active substance is prepared in a proprietary automated synthesiser unit. The synthesiser module is computer-controlled. A fluid path for synthesis is provided in the form of a single use cassette (FASTlab). The cassette contains 3 reagent vials and 3 solid phase cartridges. Two other reagent vials are supplied separately as they have a recommended storage temperature of 2-8°C. These 2 vials are inserted into the cassette on the day of production.

Fluciclovine (^{18}F) is produced in a continuous operation from the precursor AH113487. Due to the radioactive nature of the process, and the short half-life of [^{18}F] fluorine, intermediates are not isolated and there is no opportunity for operator intervention or in-process testing. Control of the synthesis of fluciclovine (^{18}F) from the precursor is achieved through the automated synthesis platform, which is pre-programmed with synthesis parameters optimised for the process. On-board detectors record transfers of radioactivity through the fluid path at critical points and monitor temperature and pressure as appropriate so that the operator may track the progress of the synthesis.

The active substance fluciclovine (^{18}F) progresses immediately to purification, formulation and dispensing as the finished product within a single, continuous operation. Validation of the manufacturing process for fluciclovine (^{18}F) is therefore described as part of finished product validation.

The characterisation of the active substance is in accordance with the EU guideline on chemistry of new active substances.

As mentioned, the manufacture of the active substance and finished product takes place in a single, continuous process. The active substance is not isolated at any point. Therefore, relevant information about impurities is given only for the finished product.

For the same reason, information for the container closure system is provided only for the finished product.

Specification

As the manufacture of the active substance and finished product takes place in a single, continuous process, and the active substance is not isolated in any point the specification of the active substance is the same as the finished product.

Stability

For the same reason as above, all information on stability is provided for the finished product.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Axumin is formulated as a sterile solution for injection containing 3,200 or 1,600 MBq fluciclovine (^{18}F) per millilitre at calibration date and time. Calibration date and time is equal to the end of synthesis (EOS) date and time. The EOS time is the time that synthesis, purification and formulation of the product is complete and is recorded in the batch record. Axumin is presented in a multi-dose vial of capacity 10 ml containing between 1 and 10 ml of product. The maximum injection volume of undiluted product is 5 ml. The content of fluciclovine is not more than 2 µg/ml. The pH of the solution is between 3.5 and 6.0.

The active substance, fluciclovine (^{18}F) is produced as an aqueous solution in the automated synthesis process. It is not isolated or tested following synthesis but is directly formulated into the finished product. The active substance has been proven to be stable over a wide range of radioactive concentrations in the chosen finished product formulation.

The finished product contains hydrochloric acid (from the active substance synthesis process) and sodium hydroxide (for pH adjustment) in sodium citrate buffer.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. 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.

Information is presented on formulations used for both clinical and pre-clinical studies. A summary and comparison of the manufacturing process, composition and quality profile of different formulations is presented and it is justified that the differences in the formulations used during development and proposed for manufacture are not relevant to safety and efficacy.

The manufacturing process development covers the manufacturing process steps related to purification of the radioactive active substance and formulation into the finished product dispensing solution suitable for sterilising filtration.

The pH of the product is controlled within the range of 3.5 to 6.0 by the inclusion of citrate buffer in the formulation. This pH range is relatively low for an injectable product however considerable clinical experience with the product has not indicated a significant safety concern related to this low pH. Osmolality measured using a freezing point osmometer is around 520 mOsm/kg.For clinical trials the strength (radioactive concentration) of the finished product varied from batch to batch depending on the number of doses required and planned injection schedule.

For marketed product two fixed strengths are proposed – 1,600 and 3,200 MBq/ml. Two processes are proposed to achieve the fixed strength:

1. Control of the amount of radioactivity entering the synthesis process in order that the solution of fluciclovine (^{18}F) obtained at the end of the FASTlab process has the correct radioactive concentration.

2. Variable amount of radioactivity for synthesis and dilution of the FASTlab solution to the correct radioactive concentration.

Process validation data is presented for both strengths using the first method and for 1,600 MBq/ml strength for the second method.

It is proposed to manufacture the product by sterile filtration although there is some evidence that the product would be stable to the effects of steam sterilisation. This has been justified on the basis that sterile filtration is an established and accepted manufacturing process for short-lived PET radiopharmaceuticals, even when they are stable to autoclaving. Fluciclovine (^{18}F) solution for injection will be made and used within a very short period of time, with a maximum shelf life of 10 hours, meaning that there is a very low risk of sterility issues. Therefore, the marketed product will be manufactured using aseptic processing with sterile filtration rather than terminal sterilisation by autoclaving. This was considered satisfactory.

The primary packaging is Type 1 glass vial, chlorobutyl rubber closure and aluminium overseal. The material complies with Ph. Eur. and EC requirements. Stability studies have been carried out which demonstrate that the quality of fluciclovine (^{18}F) solution for injection is maintained over the maximum shelf life of 10 hours after end of synthesis. The compatibility of the finished product with the container closure system has also been investigated through a study of leachables arising from the manufacturing process. It was considered that the choice of the container is adequate for the intended use of the product.

Manufacture of the product and process controls

Axumin is manufactured in two manufacturing sites.

Steps up to formation of the active substance by acid deprotection of the labelled intermediate are considered in the manufacture of the active substance section. The manufacturing process of the finished product consists of 5 main steps. The firsts steps of the manufacturing process of the finished product are conducted in the same automated synthesis module FASTlab and then the concentrated solution obtained at the end of the synthesis is transferred to a dilution/dispenser module where it is diluted to the nominal strength (if needed), sterilised by filtration and aseptically dispensed into the pre-sterilised closed vials (two different methods are used depending on the manufacturer: Method 1 and Method 2); filling of the vials by puncturing the rubber stoppers which is considered a non-standard procedure for sterile solutions but is commonly used and has been authorised in recent procedures for very short lived radiopharmaceuticals.

The suitability of the dispensing fluid path system working in cleanroom class C for Method 1 used in the sterilisation by filtration and aseptically dispensing into the pre-sterilised closed vials was discussed in detail. The issue was that only a fully closed system can be operated in a cleanroom class C. However doubts whether the dispensing fluid path system could be considered a closed system were raised, especially in view to the demount of the filled product vials from the dispensing fluid path. Based on the assurance from a local competent GMP-authority responsible for the manufacturing site using the dispensing fluid path system that the local manufacturing process is considered as a closed procedure (for which clean room class C is sufficient). It was agreed that the use of the dispensing fluid path system in a clean room class C can be accepted. A risk assessment for the risk of microbiological product contamination using manufacturing Method 1 with the dispensing fluid path device installed in cleanroom class “C” without final sterilization by heat of the finished product vials has been provided and it has been considered satisfactory.

Process validation has been conducted at both manufacturing sites and included media fill studies, pre-sterilisation bioburden (in this kind of products bioburden before the sterile filtration cannot be done in routine production batches), qualification of sterilising filters and manufacturing of six batches at one of the manufacturing sites and three batches in the other one.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (radiochemical identification (TLC, IC), radionuclide identity by gamma spectroscopy (Ph. Eur.), half-life determination (Ph. Eur.)), assay (radioactive concentration at end of synthesis (Ph. Eur.)), chemical purity tests (IC, GC, and spot test), physical measurement (pH (Ph. Eur.)), radiochemical purity (thin layer chromatography, IC), microbiological tests (Ph.Eur.), and periodic quality indicator test (Ph. Eur.).

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 identity of testing fluciclovine (^{18}F), chemical purity, and residual solvents has been presented.

Batch analysis results are provided for 12 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 3 commercial batches per strength from the two manufacturers of finished product stored at 25 ±2 °C were provided. Each batch was tested immediately after end of synthesis and then 10 hours later. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. All batches were stored upright during the shelf life which reflects the normal usage of the product. Samples were tested for appearance, content of fluciclovine and related substances, pH, and radiochemical purity. The analytical methods used were the same as for release and were stability indicating.

Supportive stability data was provided for three batches manufactured in a third manufacturing site. The batches were stored at a range of temperatures from 5 °C to 50 °C. Each batch was tested immediately after end of synthesis and then 8 hours later. The synthesis process was representative of marketed product however the radioactive concentration was not fixed to a specific strength. The batches were only tested for the key parameter of radiochemical purity (using the thin layer chromatography method).

No change in the appearance of the finished product at end of shelf life was observed for any batch tested. Storage temperature and container closure system have no impact in stability. All batches met the acceptance criteria for radiochemical purity (RCP) at the end of shelf life. The data demonstrated that the RCP will remain within the acceptance criteria over the shelf life of the product and that no specific control of storage temperature is required.

The stability of Axumin was demonstrated for up to 8 hours for the lower strength of 1,600 MBq and for 10 hours for the higher strength of 3,200 MBq in view of the radiochemical and radiophysical stability. However the difference between 8 and 10 hours is only a result of the radioactive decay because in the case of the lower strength after 8 hours not enough fluciclovine (^{18}F) is left for one dose.

Multi-dose injections without a microbiological preservative demand a strict aseptic handling during withdrawal, because otherwise the risk of microbiological contamination cannot be excluded. The short shelf life of not more than 10 hours and the fact that Axumin as aqueous solution does not contain in its composition elements which support bacterial grow help to preserve product sterility but they cannot guarantee it. Therefore, the following information highlighting to the user their responsibility in respect of the microbiological stability after first opening is included to the Summary of Product Characteristics.

"Chemical and physical in-use stability has been demonstrated for the 1600 MBq/mL and for the 3200 MBq/mL strengths for 8 hours and 10 hours, respectively.

From a microbiological point of view, unless the method of opening / dose withdrawal / dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user."

Based on available stability data, the proposed shelf-life of 8 hours from the time of calibration for the 1,600 MBq/ml strength and 10 hours from the time of calibration for the 3,200 MBq/ml strength as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance, precursor and finished product has been presented in a satisfactory manner. The radiolabelled active substance cannot be isolated as it is synthesized *in situ* during the manufacture of the finished product. The manufacturing process is a continuous, highly automated process that uses ^{18}F fluoride and a non-radioactive chemical precursor to produce fluciclovine (^{18}F). As required by the guideline on radiopharmaceuticals the non radioactive "chemical precursor" for the synthesis of PET radiopharmaceuticals complies with the Note for Guidance on Summary of Requirements for Active Substances in Part II of the Dossier (CHMP/QWP/297/97 Rev. 1). 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.

2.2.5. 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.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

To support the non-clinical aspects of the application, the applicant submitted data from the literature and non-clinical studies, which were generally performed according to GLP. Some of the studies were performed using the finished product formulation proposed for commercial manufacture. The species used for the in vivo investigation for PK and PD were mice, rat, doga and monkey. Toxicity studies were conducted in rats, dogs and monkey species. The influence of the major fluciclovine-related substance OHACBC on the pharmacodynamic activity and or the uptake of fluciclovine was investigated in human cancer cell lines (in-vitro) and in monkey, dog and rat (in-vivo).

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

In-vitro studies

Study P060612: Uptake of FACBC and FDG by Human Prostate Cell Lines.[9]

[9] Okudaira H, Shikano N, Nishii R, Miyagi T, Yoshimoto M, Kobayashi M, Ohe K, Nakanishi T, Tamai I, Namiki M, Kawai K. Putative Transport Mechanism and Intracellular Fate of Trans-1- Amino-3-18F-Fluorocyclobutanecarboxylic Acid in Human Prostate Cancer. J Nucl Med. 2011; 52: 822-829.

The aim of the study was to measure fluciclovine (anti-FACBC) and FDG uptake using various human prostate adenocarcinoma cell lines (DU145, PC-3, MDA PCa 2b, LNCaP, and 22Rv1) and normal prostate epithelial cells (PrEC) and to compare the results between cell types and test substances. ^{14}C-labelled (not ^{18}F-labelled) substances were used in this study.

The amount of [^{14}C]FDG uptake in many cell lines tended to increase with the incubation time, as did that of [^{14}C]fluciclovine in the normal epithelial cell line PrEC, while the amount of [^{14}C]fluciclovine uptake in prostate cancer cells was already high at the 5-minute incubation time point and tended to increase slightly after the 15-minute incubation time point (LNCaP, PrEC). Also, the uptake amount of [^{14}C]fluciclovine tended to reach the maximum at 5 to 30 minutes before beginning to decrease (DU145, PC-3, 22Rv I, MDA PCa 2b; Figure 2.1.1).

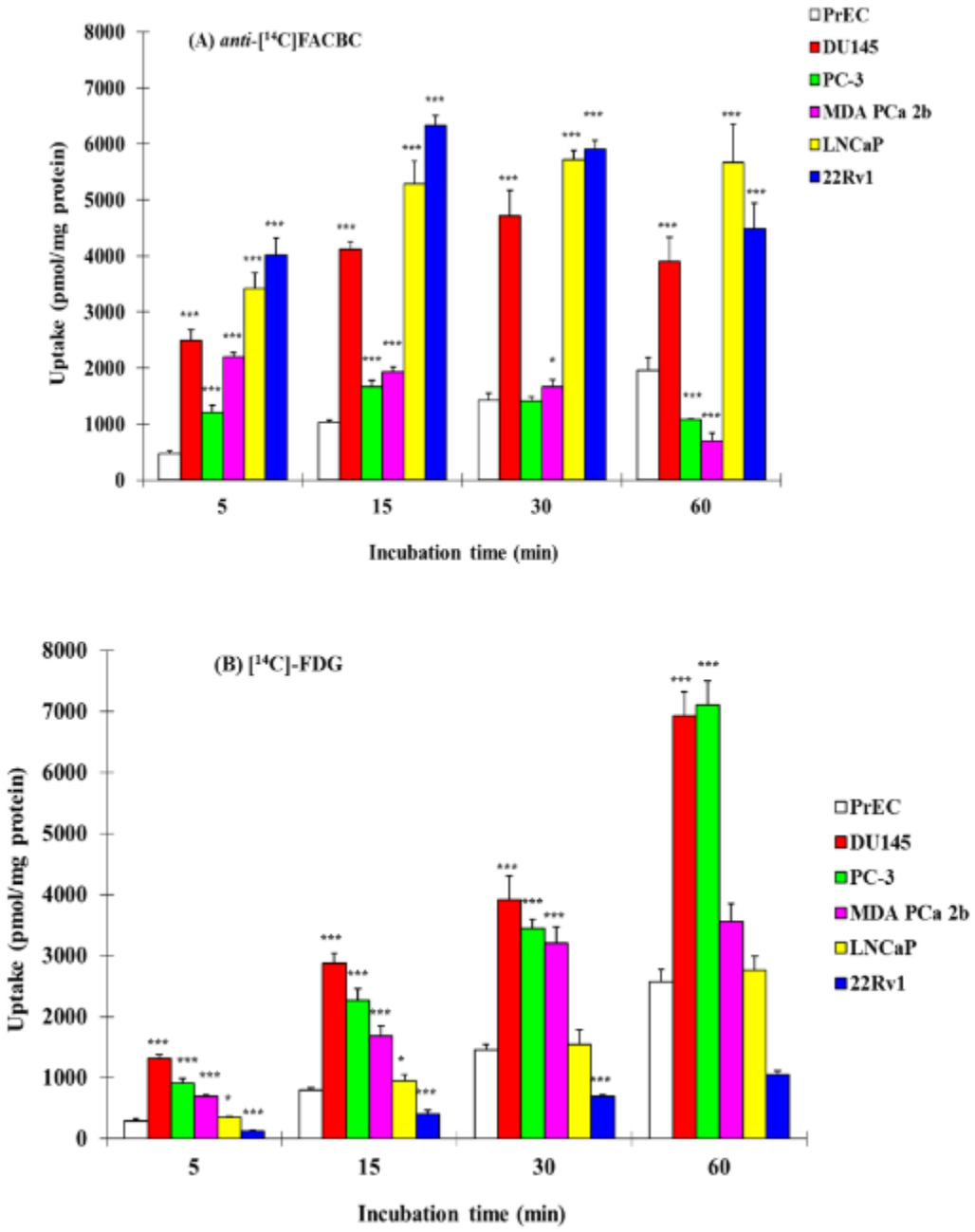
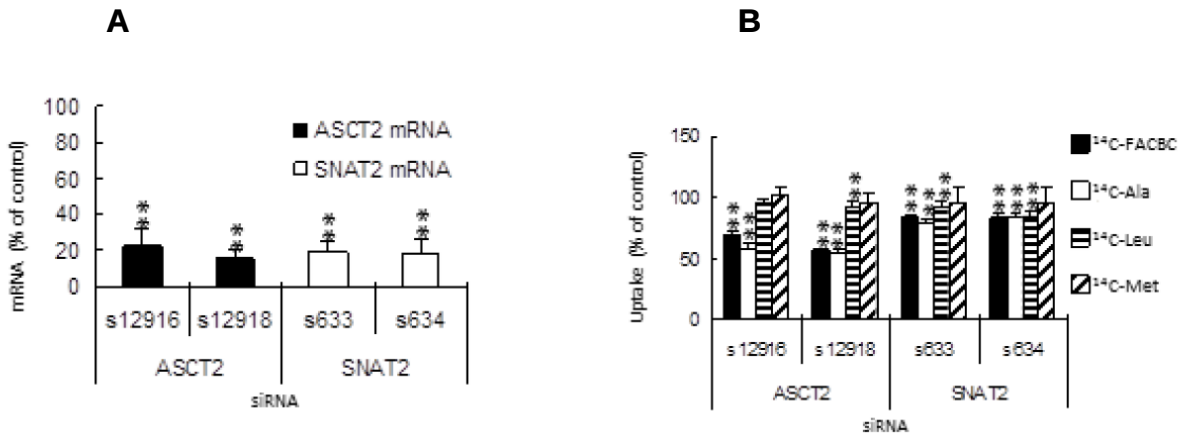


Figure 3: Uptake of [14C]-fluciclovine (here: anti-[14C]FACBC) and [14C]-FDG in human prostate adenocarcinoma cells and normal prostate epithelial cells

Significantly different from PrEC (Aspin-Welch's test or Student's t-test , *: p<0.05, ***: p<0.001)

Transporter mechanism for the update of fluciclovine

In order to further evaluate the involvement of the system ASC and system A amino acid transporters in the uptake of fluciclovine by PCa cells, Okudaira and colleagues (2011) silenced ASCT2 and SNAT2 (sodium-coupled neutral amino acid transporter 2) expression in DU145 cells using gene specific siRNA. AAT mRNA was quantified using quantitative real-time polymerase chain reaction (qRT-PCR).



**P<0.01

Figure 4: Effects of ASCT2 or SNAT2 knock-down on [14C]-fluciclovine transport in the DU145 cell line

ASCT2 and SNAT2 expression was effectively silenced using the appropriate siRNA (Figure 2.1.8A): [^{14}C]-fluciclovine uptake was significantly decreased in the presence of 2 different ASCT2-specific siRNAs (58% and 69% compared to controls) and to a lesser extent, in SNAT2 knock-down cells (83% of controls) (black bars in Figure 2.1.8B).

In-vivo studies

Study Report K36-EF001: Assessment of N MK36 Accumulation in Tumor (DU 145)

Fluciclovine distribution was investigated in male nude mice bearing subcutaneously implanted human prostatic carcinoma cells (DU145). Tumour–to–muscle, tumour–to–blood and tumour– to–urine ratios were calculated. Results are shown in the Table below.

Table 1: Tumour-tissue accumulation ratios of fluciclovine (18F) in mice bearing subcutaneously implanted human prostatic carcinoma cells (DU145)

Time	**5 mins**	**30 mins**	**120 mins**
Ratio (% ID/g)	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Tumour: blood	2.06 ±0.83	2.51 ±0.34	2.48 ±0.62
Tumour: muscle	4.35 ±1.48	2.46 ±0.14	1.73 ±0.41
Tumour: urine	5.76 ±9.76	0.31 ±0.19	0.28 ±0.18

The tumour–to–blood ratio increased from 2.06 to 2.51 % ID/g within the first 30 minutes after administration. No clear change was observed thereafter. In contrast, the tumour–to–muscle ratio was already maximal after 5 minutes, declining with time to 1.73 % ID/g after 120 minutes.

In vivo study in tumour bearing rats: Oka S, Hattori R, Kurosaki F, Toyama M, Williams LA, Yu W, Votaw JR, Yoshida Y, Goodman MM, Ito O. (2007) A preliminary study of anti-1-amino-3-18f-fluorocyclobutyl-1- carboxylic acid for the detection of prostate cancer.

The distribution of fluciclovine in tumour tissue compared with normal tissues was investigated in tumor bearing male rats. Athymic F344 rats were inoculated with human prostate cancer cells (DU145) into the ventral prostate (OPCT rat model) and the biodistribution of fluciclovine (^{18}F) was determined 3-4 weeks later.

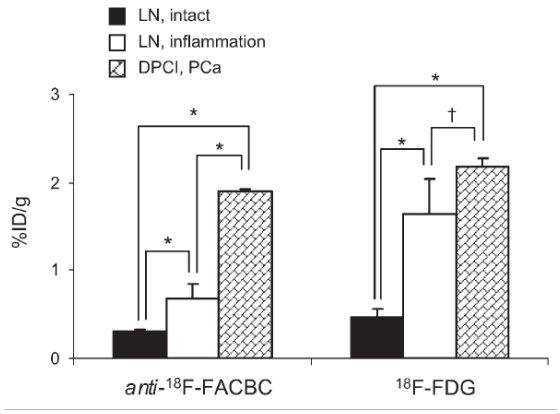
Fluciclovine (^{18}F) or [^{18}F]-FDG (7.4 MBq) was administered i.v. to anaesthetized F344 nude rats inoculated with human prostate cancer cells (DU145). Tissue distribution was determined after 15 and 60 minutes (n=3 animals per group/time-point) by counting of the radioactive decay in the respective tissues. Tissue and body fluids were weighed. For each measurement sample the radioactivity distribution (% ID) was determined, adjusted for weight (% ID/g) and the tumour–to–tissue ratio calculated. The tumour–to–tissue ratio for a selection of normal tissues (lymph node, bone, muscle, brain and urine) is presented in the table below.

Table 2: Tumour-tissue accumulation of fluciclovine (^{18}F) and [^{18}F]-FDG in the OPCT rat model

Tissue	Lymphe nodes		Bone		Muscle		Brain		Urinary bladder	
	%ID/g								%ID/mm^3	
Tracer/ Time	FDG	Fluci	FDG	Fluci	FDG	Fluci	FDG	Fluci	FDG	Fluci
15 min	1.3	3.32	1.9	2.4	5.1	5.1	0.5	8.5	0.0	0.7
60 min	1.5	4.13	1.8	2.8	7.1	3.2	0.4	4.1	0.0	0.5

Fluci = fluciclovine; ID = injected dose; LN = lymph nodes

To assess the potential of fluciclovine (^{18}F) to differentiate between PCa tissue and lymphadenitis and PCa and benign prostatic hyperplasia (BPH), the uptake of fluciclovine (^{18}F) and [^{18}F]-FDG were compared, as outlined above, in rat models of BPH and dual PCa and inflammation (DPCI). Dual prostate cancer and inflammation was induced in male Copenhagen rats (n=3) inoculated with MLLB2 cells (malignant rat prostate tumor cell line) and dosed with streptozotocin. Results are presented in the figures below.



*p < 0.01

Figure 5: Comparison of uptake of anti-^{18}F-FABC and ^{18}F-FDG at 60 min after injection into normal popliteal lymph node (LN, intact), popliteal lymphadenitis (LN, inflammation) and subcutaneous PCa

Studies with OHACBC

The influence of the major fluciclovine related substance OHACBC on pharmacodynamic activity and/or the uptake of fluciclovine was investigated *in-vitro* in human cancer cell lines and in *in-vivo* in monkey, dog and rat. Based on published and own data the SW1088 cell line was used, since in this cell line [^{14}C]-fluciclovine uptake was highest compared to the other cell lines tested. In SW 1088 cells equal amounts of [^{14}C]-fluciclovine and [^{14}C]-OHABC result in an increased accumulation of [^{14}C]-fluciclovine within the cells compared to [^{14}C]-OHACBC. In comparison with [^{14}C]L-Methionine uptake, it was shown that [^{14}C]-fluciclovine uptake is very low compared to the uptake of an essential amino acid and the [^{14}C]-OHABC uptake appears to be non-existent. Furthermore, the ability of [^{14}C]-OHACBC to inhibit the cellular uptake of [^{14}C]-fluciclovine was investigated in DU 145 cells. The inhibitory effect of OHACBC was investigated by determination of the IC_{50}, which was found to be 850 µM.[10]

Secondary pharmacodynamic studies

Study No P070305: To investigate potential secondary pharmacological effects of fluciclovine

MDR1, MRP4 and BRCP

To assess the potential for fluciclovine to act as a substrate for the ABC transporters MDR1 and BCRP, [^{14}C]-fluciclovine uptake was investigated at 2, 5 and 10 minutes, with an additional 1- minute time-point for BCRP (n=3 per time-point). The uptake of [^{14}C]-fluciclovine by the MDR1 vesicles was not considered significantly different from the negative control at all 3 time-points, with an MDR1-mediated uptake value of 1.1 pmol/mg protein at 2 minutes. By comparison MDR1- mediated uptake of the standard radiolabelled tracer [^{3}H]-verapamil was 15.3 pmol/mg protein at 2 minutes.

Uptake of [^{14}C]-fluciclovine by BCRP vesicles was assessed in the same manner and was already maximal by 1 minute, although the uptake in negative control vesicles was higher at all time-points. Km for [^{14}C]-

[10] Ono M, Oka, S, Okudaira H, Schuster DM, Goodman MM, Kawai K, Shirakami, Y. Comparative evaluation of transport mechanisms of trans-1-amino-3-[^{18}F]fluorocyclobutanecarboxylic acid and L-[methyl-^{11}C]methionine in human glioma cell lines. [2013]

fluciclovine binding was calculated as 7.2 ± 1.3 mM and 1.3 ± 0.6 mM for control and BCRP vesicles, respectively. Fluciclovine inhibited the binding of digoxin to MDR1 in a concentration-dependent manner with an IC_{50} value of 3.3 mM. In the case of BCRP, fluciclovine had no effect on the uptake of E3S.

The binding of fluciclovine to the MRP4 transporter was investigated by conducting a [^{14}C]- fluciclovine uptake assay at 2, 5 and 10 minutes (n=3 per time-point). MRP4-mediated uptake was 2.8 and 4.1 pmol/mg protein at 2 and 5 minutes, respectively. In comparison to the MRP4-mediated uptake of [^{3}H]- estradiol-17β-D-glucuronide (E2- 17βG) was calculated as 314.5 pmol/mg protein.

OAT1, OAT3, OCT2 and OATP1B1

To determine whether fluciclovine is a substrate for the renal uptake transporters OAT1, OAT3 and OCT2, [^{14}C]-fluciclovine (10 µM) uptake was investigated at 2 - 60 minutes (n=3 at each time-point). Competitive binding data obtained with [^{3}H]-PAH (1 µM) in the presence of increasing concentrations of unlabeled fluciclovine (1 - 5 mM) showed that fluciclovine inhibited the binding of PAH to OAT1 in a concentration-dependent manner with an IC_{50} of 4.0 mM (Figure 2.2.1, Panel B). Each bar represents the mean±SD (n=3).

For OAT3 and OCT2, [^{14}C]-fluciclovine (10 µM) uptake was comparable between the transfected cells and the negative control at shorter incubation periods (2 – 10 minutes), peaked at 15 minutes (11.74 ± 0.34, 9.14 ± 0.20 and 9.80 ± 0.31 nmol/mg protein for negative control, OAT3 and OCT2 respectively), and declined at a faster rate in the transfected cells thereafter. The binding affinity of fluciclovine binding to these drug transporters was investigated and Km values were calculated (values were fitted by using a Michaelis-Menten Plot) as 340 ± 37 µM, 374 ± 9 µM and 275 ± 30 µM for negative control, OAT3 and OCT2, respectively.

In order to investigate whether fluciclovine is a substrate for the hepatic uptake SLC transporter OATP1B1 radiolabelled tracer uptake assays were performed using the transfected cell line HEK/OATP1B1 and mock transfected cells as before (n=3 per time-point). [^{14}C]-Fluciclovine uptake was comparable between the transfected cells and negative control at all time-points; at 15 minutes 9.49 ± 0.15 and 11.00 ± 0.09 nmol/mg protein for OATP1B1 and negative control, respectively.

Study AL-4114-G: Investigation Of The Binding Properties Of ACBC, *anti*-FACBC And *anti*-OHACBC To Various Receptors

A very low level of inhibition of 10µM ligand binding to the adrenergic, dopamine, GABA and glycine receptors was observed (0.00% – 5.66%) for 3mM fluciclovine. Differing levels of inhibition of binding to specific ligand binding sites on the glutamate receptor were observed, ranging from 6.29% to 67.51% for the NMDA glycine binding site. Similarly for OHACBC, ligand binding inhibition for the adrenergic, dopamine, GABA and glycine receptors ranged from 0.00% to 13.36%, whilst the maximal inhibitory effect on the glutamate receptor was 27.82% for the NMDA agonist binding site.

Safety pharmacology programme

Cardiovascular System

In vitro-studies

Two in vitro studies were performed to evaluate the effects of fluciclovine (anti-FACBC) and its major related substance OHACBC on hERG channel currents (Studies: P070305 and 081010.DPY). Both tests used human embryonic kidney 293 (HEK293) cells for stable hERG channel expression. No significant effects on hERG current were observed.

In vivo studies

Cardiovascular system

Three separate in vivo studies in telemetered dogs (Studies 000726, 2789-020 and combined Cardiovascular and Pulmonary study G465536A),were performed to evaluate potential cardiotoxic effects of fluciclovine at intravenous dosages up to 1000 µg/kg. No significant effects on any parameter measured were observed.

Respiratory system

Beside study G465536, mentioned above, two rat studies (Studies 000626 and 2789-019) were performed to evaluate effects of fluciclovine on the respiratory system. No significant findings were observed.

Central nervous system

To evaluate effects of fluciclovine on the CNS two studies in the rat (Studies 000526 and 2789-021) were performed. A NOAEL of fluciclovine on the CNS in rats was determined as 1000 µg/kg.

Pharmacodynamic drug interactions

The applicant did not submit studies on pharmacodynamic drug interactions (see non-clinical discussion).

2.3.3. Pharmacokinetics

Pharmacokinetic studies have been performed in-vitro and in rats, dogs and monkeys following single dose intravenous application of the test substance.

Absorption

The applicant did not present studies on absorption (see non-clinical discussion).

Distribution

Rat

After single intravenous administration of ^{14}C-OHACBC to a male rat at a dose of 0.15 mg/kg, the radioactivity concentrations in the eyeball, cerebellum, cerebrum and fat were lower than those in the plasma (72.8 ng eq./mL), and the radioactivity concentrations in the other tissues were comparable or higher than those in the plasma, being 0.91 to 12.69 times those in the plasma at 1 h after administration. At 336 h after administration, radioactivity in the whole body decreased and the radioactivity concentration in tissue was comparable or higher than that in the plasma. The percentage distributions of radioactivity in the skeletal muscle, skin and the other tissues were 7.95% of the dose, 2.35% and 1% or less, respectively.

Study No. K36-PD0002 Distribution and Excretion Following Single Intravenous Administration of Fluciclovine (^{18}F) in Rats

Tissue distribution of fluciclovine (^{18}F) after single dose administration was investigated in male and female rats. Each rat (n=3/ sex and timepoint) was intravenously administered with 0.2 mL of test article containing 18.5 MBq of fluciclovine (^{18}F) and tissue distribution was determined with PET in the respective tissue samples at the following time points: 5 min, 30 min, 1 hr, 3 hr, 6 hr, 16 hr, 168, and 336 hr.

For both male and female rats, the radioactivity distribution ratio was found to be the highest in muscle at all the time points examined. The distribution ratio was also high in skin, blood, liver, and small intestine

compared with other organs and tissues. Considering the radioactivity distribution ratio per unit weight, the highest uptake was seen in the pancreas for both male and female rats at all time points examined. Uptake per unit weight was also greater than 1% ID/g in thymus gland, kidney, and bone marrow at many of the examined time points. The radioactivity distribution ratios per unit weight of muscle, skin, blood, liver, and small intestine, in which radioactivity distribution ratio was found to be high compared with the other organs and tissues, were not higher than the radioactivity distribution ratios per unit weight of other organs and tissues. Thus, the relatively high radioactivity distribution ratios observed in those organs and tissues are likely a result of high organ or tissue to body weight ratios rather than a significant difference in specific tissue retention.

Although, some differences between between both sexes can be seen the overall pattern of distribution is similar in both males and females. Uptake in the testes and ovaries was relatively low (maximum of 0.65% ID seen in testes at 3 hours reducing to 0.53% ID by 16 hours, ovaries maximum was 0.16% ID after 5 minutes and was not detected at 16 hours). Retention in the uterus was also low (0.59% ID at 5 minutes dropping to 0.13% ID at 16 hours).

Study No. P070415: Distribution, Excretion and Metabolism after Single Intravenous Administration of [^{14}C]Fluciclovine to Rats

Tissue distribution of fluciclovine (^{14}C) after single dose administration was investigated in male and female rats. Each rat (n=3/ sex and timepoint) was intravenously administered with 1 mL/kg of test article containing 332 kBq/kg of fluciclovine (^{14}C) and tissue distribution was determined by liquid scintillation counting of the respective tissue samples at the following time points: 168, and 336 hr.

In male rats, the radioactivity distribution ratio per tissue weight 168 hours after administration was highest in the pancreas, followed by the bone marrow, thymus, kidney, spleen, urinary bladder and heart. At 336 hours after the administration, the radioactivity distribution ratio per tissue weight was the highest in the pancreas, followed by the urinary bladder, skin, eyeball, submaxillary gland, muscle, small intestine, mesenteric lymph node, bone, stomach, prostate, large intestine and harderian gland. No radioactivity was detected in other tissues.

In female rats, the radioactivity distribution ratio per tissue weight 168 hours after administration was highest in the pancreas followed by the stomach, uterus, eyeball, muscle and skin**.** At 336 hours after the administration, no radioactivity was detected in any tissues.

Study No. K36-PD0003: Metabolite Analysis, Distribution in Blood Cells, and Plasma Protein Binding Following Administration of Fluciclovine (^{18}F) to Rats

Distribution into blood cells and plasma protein binding was determined in male and female rats. Each rat (n=3/sex and timepoint) was intravenously administered with 0.2 mL of test article containing 18.5 MBq of fluciclovine (^{18}F). Blood samples were taken at the following time points: 5 min, 1 hr and 3 hrs. Distribution into blood cells and plasma protein binding was determined by gamma counting followed by calculation of the distribution within the respective share.

About 30% of total radioactivity distributed into blood cells at all time points investigated. No sex differences were noticed. No plasma binding was detected.

Dog

After single intravenous administration of ^{14}C-OHACBC to a male dog at a dose of 0.15 mg/kg, the radioactivity concentrations in the thigh bone and eyeball were lower than those in the plasma (2.1 ng

eq./mL), and the radioactivity concentrations in the other tissues were comparable or higher than those in the plasma, being 1.05 to 10.57 times those in the plasma at 336 h after administration. The percentage distributions of radioactivity in the skeletal muscle and the other tissues were 2.55% of the dose and 0.5% or less, respectively.

Monkey

Table 3: Results of Study No. AE-5775

Study ID	Species	N	Dose (mg/kg)	Route	C_0 (ng eq./ml)	AUC (µg eq. h/ml)
AE-5775	Rat	1	0.15	I.V.	272.6	2.93
AE-5775	C. monkey	1	0.15	I.V.	488.1	2.29

Study ID	Species	N	Dose (mg/kg)	Route	$t_{½}$, el (hrs)	Vd (L/Kg)	Clt (ml/hrs/kg)
AE-5775	Rat	1	0.15	I.V.	6.5 (I) 74 (II)	4.89	51.2
AE-5775	C. monkey	1	0.15	I.V.	3.6 (I) 68 (II)	4.19	65.4

After single intravenous administration of ^{14}C-OHACBC to a male monkey at a dose of 0.15 mg/kg, the radioactivity concentrations in the thigh bone and eyeball were lower than those in the plasma (2.4 ng eq./mL), being 0.58 and 0.25 times those in the plasma, respectively, and the radioactivity concentrations in the other tissues were comparable or higher than those in the plasma, being 1.04 to 13.88 times those in the plasma at 168 h after administration. The percentage distributions of radioactivity in the fat, skeletal muscle and the other tissues were 1.76% of the dose, 0.86% and 0.3% or less, respectively.

Study No. P070417: Radioactivity Concentrations in Blood and Excretion after Single Intravenous Administration of [^{14}C]Fluciclovine to Monkeys

Cynomolgus monkeys received 332 KBq/kg [^{14}C] fluciclovine via intravenous injection. Blood samples were collected at the following time points: 5, 15, 30 minutes and 1, 3, 6, 24, 48, 72, 120, 168 and 240 hours after the administration. The radioactivity in the blood was measured using liquid scintillation counting. The following parameters were obtained:

Table 4: Results obtained in study P070417

Study ID	Species	N	Dose	Route	t½, el	C5min (% ID/g)	AUC (%IDh/g)
P070417	C. monkeys	3	332 KBq/Kg	I.V.	35.4	0.042	0.505

			^{14}C-fluciclovine				

Metabolism

Study No. K36-PD0003: Metabolite Analysis, Distribution in Blood Cells, and Plasma Protein Binding Following Administration of Fluciclovine (^{18}F) to Rats

Plasma and urinary metabolites were analysed in male and female rats. Each rat (n=3/sex and timepoint) was intravenously administered with 0.2 mL of test article containing 18.5 MBq of fluciclovine (^{18}F). Blood and urine samples were taken at the following time points: 5 min, 1 hr and 3 hrs. The results are presented in Table 5 and Table 6.

Table 5: Ratios of peaks in Plasma

	Ratios of Peaks in RLG of Sample for Plasma Metabolite Analysis (Male) (%)		
Peak	5 minutes after administration Mean ±SD	1 hour after administration Mean±SD	3 hours after administration Mean±SD
	0.01± 0.00		
UK3	0.04±0.01	0.02± 0.00	0.02± 0.00
UK4	0.04± 0.01		
FACBC*	6.00± 1.18	2.78± 0.15	2.65±0.10
Other**	0.02± 0.00	0.01± 0.00	0.02± 0.00

	Ratios of Peaks in RLG of Sample for Plasma Metabolite Analysis (Female) (%ID)		
Peak	5 minutes after Mean ± SD	1 hour after Mean ±SD	3 hours after administration Mean ± SD
UK1	0.01± 0.00		
UK3	0.04± 0.01	0.02± 0.00	0.01± 0.00
UK4	0.04± 0.00		
FACBC*	5.78± 0.44	2.91± 0.25	2.74± 0.38
Other**	0.01 ± 0.00	0.01± 0.00	0.01 0.00

Table 6: Ratios of peaks in urine after 6 hrs of collection

	Ratios of Peaks in RLG of Sample for Plasma Metabolite Analysis (%ID)	
	Male	Female
Peak	Mean ± SD	Mean ±SD
UK1	0.03± 0.00	0.03±0.01
UK3	0.02± 0.00	0.05±0.01
UK4	0.07± 0.07	0.05±0.08
FACBC*	3.54± 0.55	13.26±5.11
UK6	0.04± 0.01	0.05±0.00
UK7	0.01± 0.00	
UK8	0.01± 0.00	0.01±0.00
Other**	0.02± 0.00	0.02±0.01

Excretion

Excretion of fluciclovine was investigated in male and female rats and male Cynomolgus monkeys. In both species the main route of excretion was urinary.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity testing of fluciclovine was carried out in two rat (400127, 400326) and a dog (600126) study. No toxicokinetic measurements were performed concomitantly. A full examination including general signs, mortality, body weight, food consumption, urinanalysis, clinical chemistry/haematology and histopathology were done on day 1 post-dose and after 14 days recovery period. Study design and major outcomes are shown in Table 7.

The observed max non-lethal dose was > 1000 µg/kg (FACBC). The safety margin of the maximum non-lethal dose (1000 µg/kg) to the estimated clinical dose of FACBC was ~ 5882 x and ~ 3182 x with scaling for species differences.

Table 7: Single dose toxicity studies performed with intravenous applications of FACBC

Study ID	Species / Sex / Number / Group	Dose / iv	Observed max non-lethal dose	Major findings
400127 GLP FACBC	rat [Crl:CD(SD)] 10♀/10♂/group	2.5 ml/kg 5 ml/kg 10 ml/kg Dosing Volume 2.5 nmol/ml	> 10 ml/kg	**(5, 10) ml/kg** brain absolute weight ↓ ♂ d1 **(2.5, 10) ml/kg** lung relative weight ↓ ♀ d1 **10 ml/kg** fibrinogen concentration ↑ ♀ d1 **5 ml/kg** food consumption ↑ ♂ 4d post dose, heart absolute/relative weight ↓ ♂ d1, hemoglobin ↑ ♀ d1, eosinophil ratio ↓ ♂ d14, creatinin ↓ ♂ d14, Na^+ ↑ ♀ d14
400326 GLP FACBC	rat [Crl:CD(SD)] 10♀/10♂/group	100 µg/kg 300 µg/kg 1000 µg/kg	> 1000 µg/kg	**(100, 300, 1000) µg/kg** - α_1-globulin ↑ ♂ small d14 **1000 µg/kg** total cholesterol ↑ ♂ d1, Na^+ ↑ ♀ d14 **300 µg/kg** mean corpuscular hemoglobin ↑ ♂ d14 urea nitrogen ↑ ♂ d14, ALT ↑ ♀ d14 **100 µg/kg** mean corpuscular volume, corpuscular hemoglobin ↑♂ d14, α_2-globulin, K^+ ↓ ♂ d1

600126 GLP FACBC	dog [Beagle] 2♀/2♂/group	100 µg/kg 300 µg/kg 1000 µg/kg Dosing Volume 1 ml/kg	> 1000 µg/kg	**1000 µg/kg** white blood cell count ↑ ♂ d1 **300 µg/kg** white blood cell count ↑ ♂ d1

d = day, FACBC = fluciclovine, ↑ = increase, ↓ = decrease

Single dose toxicity testing of OHACBC was carried out in a rat study (400726). No toxicokinetic measurements were performed concomitantly. A full examination including general signs, mortality, body weight, food consumption, urinanalysis, clinical chemistry/haematology and histopathology was done on day 1 post-dose and after a 14 day recovery period. Study design and major outcomes are shown in Table 8.

The observed maximum non-lethal dose was > 1000 µg/kg (OHACBC). The safety margin of the maximum non-lethal dose (1000 µg/kg) to the estimated clinical dose of OHACBC was ~ 80 x without and ~ 43 x with scaling (body surface area) for species differences.

Table 8: Single dose toxicity studies with iv application OHACBC

Study ID	Species/ Sex/Number/ Group	Dose/Route	Observed max non-lethal dose	Major findings
400726 GLP OHACBC	rat [Crl:CD(SD)] 10♀/10♂/group	100 µg/kg 300 µg/kg 1000 µg/kg Dosing Volume 1 ml/kg	> 1000µg/kg	**1000 µg/kg** red blood cell count/hematocrit ↑ ♀, testis small right ♂ **300 µg/kg** food consumption ↑ ♀ d(4 – 11), spleen absolute/ relative weight ↓ ♀ d1, ovary absolute weight ↑ ♀ d14, triglycerides ↑ ♀, Cl^- ↓ ♀ **100 µg/kg** fibrinogen ↑ ♂, AST ↑ ♂

d = day, OHACBC = major impurity, ↑ = increase, ↓ = decrease

Repeat dose toxicity

Repeat-dose toxicity testing of fluciclovine and fluciclovine/OHACBC was carried out in rats (6336-141, 500326, 2789-017), rabbits (6336-142) and dogs (640126, 2789-018) for a maximum of 14 days. The route of application in all studies was intravenous. Two in vitro micronucleus tests and a functional observation battery-test were included into the rat studies 6336-141 and 2789-017.

Table 9: Repeated dose toxicity studies with intravenous administration of FACBC and/or OHFABC

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOAEL	Major findings

6336-141 GLP	rat (Fischer) 15♀/15♂/group [10 + 5 recovery/group]	fluciclovine / OHACBC [1 : 9] 0.04/0.36 mg/kg/d 0.2/1.9 mg/kg/d	14d + 14d recovery	0.2/1.9 mg/kg/d	**(0.04/0.36, 0.2/1.9) mg/kg/d** thyroids (mean absolute / relative / parathyroids ↓ ♂ d15, Na^+ K^+ blood urea nitrogen ↓ ♀ d8, absolute / relative neutrophils ↑, relative lymphocytes ↓ ♂ reversible d15, absolute/relative neutrophils relative lymphocyte ↑ ♀ d15 reversible d29 **(0.2/1.9) mg/kg/d** mean absolute / relative spleen weight ↓ ♂ d15, mean total protein globulin ↓, albumin/globulin ratio ↑ total protein, albumin ↓ ♀ reversible d14/29, reticulocyte count ↓ ♂ d8 reversible, red blood cells hemoglobin/hematocrit ↓ ♂, red blood cells, hemoglobin, hematocrit ♀ d8 reversible d15/29 **0.04/0.36 mg/kg/d** Ca^{2+} cholesterol ↑ ♀ d15, mean total bile acids ↑ ♀ d29 **micronucleus test** **0.2/1.9 mg/kg/d** mean MPCE per 2000 erythrocytes ↓ ♀ d29 **functional observation battery** **0.2/1.9 mg/kg/d** body temperature ↓ d14 reversible d28 **(0.04/0.36, 0.2/1.9) mg/kg/d** mean foot splay ↑ male - d1 pre-dosing

500326 GLP	rat [Crl:CD(SD)] 10♀/10♂/group	fluciclovine 100 µg/kg/d 300 µg/kg/d 1000 µg/kg/d	14d	1000 µg/kg/d	**1000 µg/kg/d** ALP ↑ ♂, AST ↓, lung unilateral mineralization vascular wall 1 control ♂ hair embolism (3 ♂, 1 ♀, 1 control ♂, 1 control ♀) liver extramedullary hematopoiesis 1 control ♂, microgranuloma 2 ♂ / 2 ♀, focal necrosis, vacuolar degeneration in centrilobular hepatocytes 1 control ♀ spleen had extramedullary hematopoiesis 2 control ♂ kidney basophilic change in tubular epithelium 1 control ♂, cyst 1 ♂ eye eyeballs retinal dysplasia (1 control ♂, 3 control ♀, 1 ♂) **injection site** perivascular hemorrhage 1 ♂, perivascular fibrosis 3 control ♀, 4 ♀ hair embolism 1 ♂, 2 ♀, 2 control ♀, cellular infiltration in vicinity of blood vessels 6 control ♀, 8 ♀ **(300, 1000) µg/kg/d** cholesterol ↑ **300 µg/kg/d** pituitary relative weight ↑ ♂, fibrinogen ↑ ♂, Ca^{2+} ↑, prothrombin time ↑ ♂, total bilirubin ↑ ♀
2789-017 GLP	rat [Crl:CD(SD)] 5♀/5♂/group 3♀/5♂/TK group	fluciclovine / OHACBC [1 : 39] 22/842 µg/kg/d dosing volume 10 ml/kg/d 43/1683 µg/kg/d dosing volume 20 ml/kg/d	14d	1000	**(0, 22, 43) µg/kg/d** liver (minimal inflammatory cell foci) **(22, 43) µg/kg/d** K^+ ↓ slight **43 µg/kg/d** body weight gain food consumption ↓ ♂ slight, ophthalmoscopy lens opacity failure of pupil to dilate 1 ♀ , red blood cell count ♂ slight, mean cell volume mean cell haemoglobin ↓ ♂ very small, PO_4^{3-} ↑ slight

6336-142 GLP	rabbit [Crl:CD(SD)] 5♀/5♂/group 3♀/5♂/ recovery group	fluciclovine / OHACBC [1 : 15] 0.025/0.385 mg/kg 0.065/0.98 mg/kg	14d + 14d recovery	0.065/0.98 mg/kg	**(control, 0.025/0.385, 0.065/0.98) mg/kg/d** **injection site** [subcutaneous tissue (hemorrhage/infiltration of few mononuclear inflammatory cells)] **(0.025/0.385, 0.065/0.98) mg/kg/d** relative monocytes ↑ ♀ d15, cholesterol ↓ ♂ d15, globulin ↓ ♂ d29 **0.065/0.98 mg/kg/d** thymus (relative weight) ↑ ♀, albumin/globulin ratio ↑ ♂ d29
640126 GLP	dog [Beagle] 3♀/3♂/group	fluciclovine 100 µg/kg/d 300 µg/kg/d 1000 µg/kg/d	14d	1000 µg/kg/d	**(100, 300, 1000) µg/kg/d** food consumption ↓ [1 ♂/1 ♀ (100µg/kg/d), 1 ♂/1 ♀ (1000µg/kg/d), 1 ♀, control /1 ♀, (1000µg/kg/d)] **injection site** hemorrhage all, cellular infiltration **1000 µg/kg/d** spleen relative weight ↓ ♀, K^+ (differences, urine) ♂, glucose (positive urine) 1 ♂ d10, total cholesterol ↑ ♀, thyroid left/right, lymphoid cellular infiltration 1 ♂ **(100, 1000) µg/kg/d** Cl^- ↓ (urine) ♂ d10 **(300, 1000) µg/kg/d** -α_2-globulin (differences) ♀ **300 µg/kg/d** epididymis relative weight ↑, ♂ neutrophil (ratio) ↑ ♀, ventricle dilation 1 ♂ **100 µg/kg/d** body weight ↓ 1 ♀ d14, reticulocyte ratio ↓ ♀, pituitary anterior lobe cyst ♂/♀, eyeball right, dysplasia in retina ♂, lung hair embolism ♀
2789-018 GLP	dog [Beagle] 3♀/3♂/group	fluciclovine / OHACBC [1 : 39] 5.4/210 µg/kg/d dosing volume 2.5 ml/kg/d 10.8/421 µg/kg/d dosing volume 5 ml/kg/d	14d	10.8 µg/kg/d	**10.8 µg/kg/d** red blood cell parameters ↓ 1 ♂/1♀ slight/small

↑ = increase, ↓ = decrease, ALP = alkaline phosphatase, AST = aspartate transaminase, d = day, MPCE = micronucleated polychromatic erythrocyte, OHACBC = major impurity

Genotoxicity

To assess the genotoxic potential of fluciclovine and the major impurity (OHACBC) several *in vitro* and *in vivo* genotoxicity studies were performed.

Table 10: Genotoxicity studies with FACBC

Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results**
900326 Fluciclovine Salmonella Reverse Mutation Plate Incorporation Assay *in vitro* GLP	TA98, TA100, TA1535, TA1537	a. (0, 1.22, 4.88, 19.5, 78.1, 312.5, 1250, 5000) µg/plate, +/- S9 b. (0, 312.5, 625, 1250, 2500, 5000) µg/plate, +/- S9	negative
970226 Fluciclovine Chromosomal Aberration Test *in vitro* GLP	CHL/IU cells	(0, 425, 850, 1700) µg/ml (10 mM) ± S9 (6 h), - S9 (24 h)	negative
940127 Fluciclovine Micronucleus Test *in vivo* GLP	rat [♂ Crl:CD(SD)]	(0, 2.5, 5, 10) ml/kg (2.5 nmol/ml)	negative
940126 Fluciclovine Micronucleus Test *in vivo* GLP	rat [♂ Crl:CD(SD)]	(0, 100, 300, 1000) µg/kg	negative

Table 11: Genotoxicity studies with OHACBC

Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range /**	**Results**

		Metabolising system	
900426 OHACBC Salmonella Reverse Mutation Plate Incorporation Assay *in vitro* GLP	TA98, TA100, TA1535, TA1537	a. (0, 312.5, 625, 1250, 2500, 5000) µg/plate, +/- S9 b. (0, 312.5, 625, 1250, 2500, 5000) µg/plate, +/- S9	negative
970326 OHACBC Chromosomal Aberration Test *in vitro* GLP	CHL/IU cells	(0, 350, 700, 1400) µg/ml ± S9 (6 h), - S9 (24 h)	negative

Carcinogenicity

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

Reproduction Toxicity

No specific reproductive or developmental toxicity studies were submitted (see non-clinical discussion). However, histological evaluations of male and female reproductive organs in dogs and rats were performed in the single and repeat dose toxicity studies and showed no abnormalities.

No fertility and early embryonic development studies have been submitted.

No embryonic and foetal toxicity studies have been submitted.

No prenatal and postnatal developmental toxicity studies have been submitted.

Toxicokinetic data

Toxicokinetic data for fluciclovine/OHACBC were assessed for the rat study 2789-017 and dog studies 640126 and 2789-018. In summary, accumulation of OHACBC was observed in rats and OHACBC and fluciclovine in dogs. However, no adverse toxic effects were derived from accumulation in repeat-dose studies.

Local Tolerance

To assess the possible irritation potential of fluciclovine, two local tolerance studies (iv and sc vascular irritancy tests) were performed according GLP in rabbits (6 ♂, Kbl: JW).

In study 700327, a single dose of 3 ml fluciclovine (dosing rate 1 ml/min) was administrated intravenously in the left V. auricularis posterior. After the histopathology examination of the injection sites 2 days post-dose a slight cellular infiltration was noted in the subcutis where saline (control) had been injected (1/3 sites).

In study 700427, a single dose of 3 ml fluciclovine (dosing rate of 1ml/min) was administrated subcutaneously in the vicinity of the left V. auricularis posterior. Immediately after injection of fluciclovine

and control, a slight subcutaneous hemorrhage (3/6 sites) was noted. Additionaly, a slight cellular infiltration was noted in the subcutis far from the V. auricularis posterior where saline (control) had been injected (1/3 sites). No further signs of toxicity concerning general signs, body weight, macroscopic and microscopic examination of the injection sites were noted.

2.3.5. Ecotoxicity / environmental risk assessment

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00), an environmental risk assessment (ERA) was submitted.

LogKow

The logKow values for fluciclovine have been estimated using computer programs (-0.61, -0.86 to -1.21). The experimental log Kow value for fluciclovine hydrochloride in an OECD study was -2.53.

Calculation of the Predicted Environmental Concentration (PEC)

In accordance with the EMA guideline for environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00), the Predicted Environmental Concentrations in surface water (PECsw) in the ERA Phase I was calculated by the Applicant using the following formula:

$$PECsw\ (mg/L) = \frac{DOSEai(mg/inh/d) * Fpen}{WASTEWinhab\ (L/inh/d) * DILUTION}$$

where:
DOSEai: maximum daily dose consumed per inhabitant (mg/inh/d)
Fpen: percentage of market penetration (default value (0.01))
WASTEWinhab: amount of waste water per inhabitant per day (default value: 200 L/inh/d)
DILUTION: dilution factor (default value: 10)

The worst-case calculation for the active substance fluciclovine, based on the highest recommended dose of 10 µg/day, resulted in a PECsw value of 0.05 ng/l, which is below the action limit of 10 ng/l.

Table 12: Summary of main study results

Substance (INN / Invented Name): fluciclovine (^{18}F)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-2.53	
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		not B
Persistence	DT50 or ready biodegradability		not P
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT		
Phase I			

Calculation	Value	Unit	Conclusion
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	$3.3 \cdot 10^{-9}$ (fluciclovine) $2.47 \cdot 10^{-7}$ (OHACBC)	µg/L	> 0.01 threshold

2.3.6. Discussion on non-clinical aspects

Pharmacodynamic activity of fluciclovine (uptake into tumour cells) was studied in-vitro and in-vivo and the results obtained support the intended clinical use. Secondary pharmacodynamic data is limited to receptor binding studies, but this is acceptable for this type of medicinal product. Safety pharmacology studies are limited to the core battery and do not reveal any specific safety risk in animal models and its intended clinical use.

Pharmacokinetic data were sparse and data on absorption was limited to toxicokinetic data. In agreement with fluciclovine's intended clinical use, distribution data showed a broad distribution within the body without pronounced accumulation in normal tissues. The major route of elimination is via the renal pathway. Fluciclovine does not appear to be extensively metabolised because the two unidentified peaks were found to be negligible.

Toxicological studies with rats and dogs have demonstrated that with a single intravenous injection no deaths were observed. Toxicity with repeated administration of up to 1000 mcg/kg/day over 14 days in rats and dogs was not observed. This medicinal product is not intended for regular or continuous administration. Long-term carcinogenicity studies have not been carried out.

Genotoxicity studies were carried out and no relevant findings were observed. No carcinogenicity studies were performed. Given the negative results from the genotoxicity studies and the intended single dose application of fluciclovine in patients, no carcinogenicity studies are necessary.

No specific reproductive or developmental toxicity studies have been conducted or are planned with fluciclovine. This is acceptable, as fluciclovine is not intended for repeated use and in women of child-bearing potential.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical pharmacologic, pharmacokinetic, and toxicological characteristics of fluciclovine have been well characterised. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

The non-clinical aspects are considered to be appropriately addressed.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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.

- Tabular overview of clinical studies

Table 13: Summary of phase I clinical studies with fluciclovine (^{18}F) solution for injection

Study No./ Sponsor/ publication	Study Design	Population	No. Subj	Study drug	Objections/endpoints
Phase I					
GE148-001 GE Healthcare Sorensen, 2013 McParland, 2013	Open label, single dose	Healthy volunteers Primary prostate cancer	6 [3M/3 F] 6	Mean dose 154 MBq Mean dose 418 MBq	Safety, biodistribution and dosimetry in HVs Safety, uptake and retention in biopsy-proven prostate cancer
NMK36-P1 NMP Asano, 2011	Open label, single dose	Healthy volunteers	6	174-201 MBq	Safety, biodistribution and dosimetry
Emory University Nye, 2007	Open label, single dose	Healthy volunteers	6 [3M/3 F]	Mean dose 366 MBq	Safety, biodistribution and dosimetry

Table 14: Phase II clinical studies

Study No./ Sponsor	Study Design	Population	No. Subj	Study drug	Objections/endpoints
GE148-002 GE Healthcare Study report	Open label, single dose	Primary prostate cancer	21	Mean dose 351 MBq	Safety and proof of concept efficacy data (***Efficacy and pharmacokinetics analyses were not performed because GE Healthcare terminated the study early for administrative reasons.***)
NMK36-PC-201 NMP Study report	Open label, single dose	Primary prostate cancer	10	94 – 288 MBq	Safety, dose ranging and proof of concept efficacy data

Study No./ Sponsor	Study Design	Population	No. Subj	Study drug	Objections/endpoints
NMK36-PC-202 NMP Study report -	Multicentre, open label, single dose	Primary prostate cancer patients at intermediate and high risk of LN involvement and patients with advanced primary disease and known metastases	68	Low dose: 127 ± 10% High dose: 270 ± 10% MBq	Efficacy assessment by diagnostic performance vs CT/bone scan; safety

Table 15: Phase III clinical studies

Study No./ Sponsor	Study Design	Population	No. Subj	Study drug	Objections/endpoints
R01 **No study report retrieved from the submission**	Retrospective collection of data from patients exposed to fluciclovine (^{18}F) for the diagnosis of cancer	Recurrent prostate cancer Primary prostate cancer Breast cancer	713	Mean dose 309 MBq (range 140-485 MBq)	Efficacy vs histopathology standard of truth Comparison to ^{11}C choline Safety
BED001/ Emory University Study report	Open label single dose, comparative study vs **indium (^{111}In) ProstaScint**	Recurrent prostate cancer	115	162 – 485 MBq	Diagnostic performance vs histology
BED001/ Bologna University Study report	Open label single dose, comparative study vs **choline (^{11}C)**	Recurrent prostate cancer	91	~ 370 MBq	Detection rate vs 11C choline

Table 16: Additional Reader Studies

Study No./ Sponsor	Study Design	Population	No. Subj	Study drug	Objections/endpoints
BED002 Reader study	Blinded image evaluation of Fluciclovine PET-CT scans from: 1. The R01 Emory University study (biopsy population) 2. Bologna University (comparison to ^{11}C choline)	Recurrent prostate cancer	105 88	- -	Fluciclovine PET-CT diagnostic performance vs histopathological standard of truth Comparison of Fluciclovine PET-CT BIE read and onsite 11C Choline PET CT scan read

Study No./ Sponsor	Study Design	Population	No. Subj	Study drug	Objections/endpoints
BED007 Reader study	Blinded image evaluation of choline (^{11}C) PET-CT scans from Bologna University	Recurrent prostate cancer	88	-	Comparison to fluciclovine BIE read from BED002

Emory study

Study Emory **R01** was a non-randomised, open-label, single arm study designed to investigate the ability of fluciclovine (^{18}F) PET-CT imaging to detect recurrence of prostate carcinoma in the prostate bed validated by pathologic analysis of prostate bed biopsies and subject follow-up.

Bologna study

This study was a non-randomised, open-label, single arm study designed to compare the ability of fluciclovine (^{18}F) PET-CT imaging to detect recurrence of prostate carcinoma with choline (^{11}C). Within-subject comparisons were used to evaluate subjects (ultrasound, MRI, CT, SPE and other PET) before and after the fluciclovine (^{18}F) scan were recorded, where available, as well as the related biopsy and surgery results and the corresponding histopathology reports were recorded for comparison with the scan findings.

BED-001 study was designed in order to retrospectively collect, pool and analyse relevant data from several clinical studies, mainly on two clinical phase III studies (**BED001 Emroy, BED001 Bologna**) and additional patients from the open access program. It was planned primarily to confirm the safety of fluciclovine (^{18}F) given intravenously and in order to allow a comparison of diagnostic performance (efficacy) analysis in the additional blinded reader studies **BED002** and **BED007**.

2.4.2. Pharmacokinetics

The pharmacokinetics, distribution and metabolism of fluciclovine (^{18}F) were evaluated as part of Studies GE-148-001 and NMK36-P1. In Study GE148-001, radioactivity in plasma and urine was assessed using standard radioactivity counting methods.

Absorption

The applicant did not submit studies on absorption.

Food effect

Oka et al showed *in vitro* that 2mM concentrations of certain amino acids, such as serine, glutamine and phenylalanine, could inhibit fluciclovine uptake and accelerate the rate of efflux from target cells[11]. The applicant did not submit studies evaluating food effect on fluciclovine imaging. All studies to date have required at least a 4 hour fast before scanning. Thus, the SmPC recommends that prior to administration of fluciclovine (^{18}F), patients should not eat or drink for at least 4 hours (other than small amounts of water for taking medicinal products) (SmPC section 4.4).

[11] Oka S, Okudaira H, Yoshida Y, Schuster DM, Goodman MM, Shirakami Y, Transport mechanisms of trans-1-amino-3-fluoro[1-14C]cyclobutanecarboxylic acid in prostate cancer cells. Nuclear Medicine and Biology 2012. 39: 109-119.

Distribution

Healthy volunteers

Two studies and one publication have evaluated the biodistribution in healthy volunteers (GE-148-001; NMK36-P1;)[12].

Fluciclovine (^{18}F) distributes immediately following administration to the liver (14% of administered activity), pancreas (3%), lung (7%), red bone marrow (12%) and heart wall (4%). There is very little brain uptake, at 1.6% (0.7% to 2.2%). With increasing time post injection (pi), uptake in skeletal muscle increases. Limited uterine uptake is noted in non hysterectomized women (1.2%; 0.3% to1.7%). Lung uptake is also apparent (7.1%; 5.2%-8.6%), but, based on comparison with washout of activity from the whole-blood samples, activity in the lung was likely due to activity in the pulmonary blood pool. In study GE-148-001, excretion of ^{18}F activity was limited and could only be detected through the renal pathway, with an average of 3.2% excreted in the urine by the last collection time point of on average 4.2 hours post-injection. No measurements of activity were performed beyond the last collection time point of on average 4.2 hours (range: 3.8 to 4.7 hours). The critical organ was the pancreas, with a mean absorbed dose of 103 microGy/MBq. The mean effective dose per unit administered activity was 22 microSv/MBq.

In study NMK36-P1, mean values for radioactivity distribution rates in organs and tissues per unit volume peaked at 3 minutes post-administration in the pancreas, 10–84 minutes in the liver, and in the muscle at 150 minutes and 220 minutes. Mean values for radioactivity distribution rates per organ and tissue were greatest in muscle at all scanning time points, followed by the liver, red marrow, and lungs. The cumulative rate of urinary excretion of radioactivity increased over time, with the mean value for the rate of urinary excretion of radioactivity from immediately post-administration to 24 hours post-administration being 5.40% injected dose (ID). Two other unidentified peaks were detected in the analysis beside fluciclovine, the dose equivalents for these peaks were 0.00500%ID and 0.0717%ID, respectively.

Fluciclovine (^{18}F) has slow and limited excretion into the urine and other differences in uptake kinetics provides some advantages over ^{18}F-choline in terms of image quality (Figure 6).

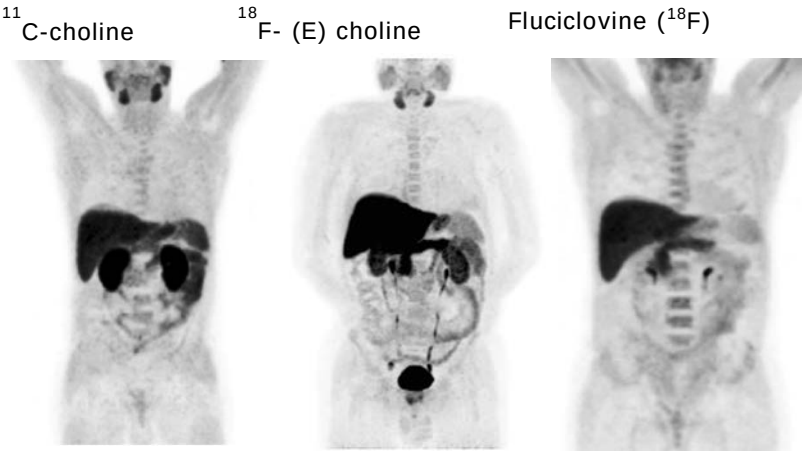


Figure 6: Image Quality of 11C- Choline, 18F- Choline and Fluciclovine

Patients with prostate cancer

[12] Nye JA, Schuster DM, Yu W, Camp VM, Goodman MM, Votaw JR. Biodistribution and radiation dosimetry of the synthetic nonmetabolized amino acid analogue anti-18F-FACBC in humans. J Nucl Med 2007. 48:1017-1020

Kinetic data in patients with prostate cancer was studied in study **GE148-001**. In addition to providing data on uptake, a comparison of uptake and efflux of tracer from the malignant lesions to uptake in healthy tissues was conducted. The results demonstrated rapid uptake of tracer into malignant tissue, reaching a plateau within 5 minutes of injection. Efflux of tracer from the tumour began within 15 minutes. In lymph node lesions, uptake was also rapid, but followed by a faster washout than in prostate tumour.

Patients with suspected recurrence of prostate cancer or metastatic disease

Patients with prior history of histologically confirmed prostate carcinoma with suspected recurrence or metastatic disease were also investigated in a pilot study on 15 patients by Schuster et al 2007[13]. Time activity curves show rapid uptake of fluciclovine (^{18}F) in known prostate carcinoma recurrence, to a maximum at 4.5 minutes with a plateau to 30 minutes, which is followed by gradual clearance (9%/min) out to 60 minutes. Regions in marrow (ilium), muscle (gluteus), and bladder reached a plateau at 4.5 minutes that remained constant throughout the imaging period.

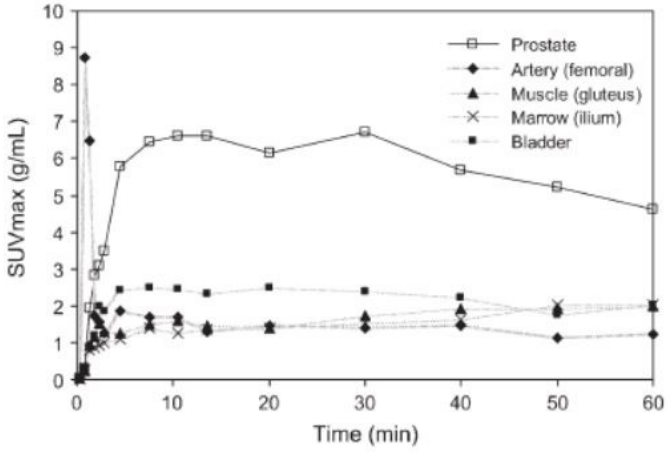


Figure 7: Time–activity curve compares uptake in known prostate bed carcinoma recurrence vs. bladder, marrow, muscle, and femoral artery

Similar findings were obtained from time–activity curves in a malignant right internal iliac lymph node.

[13] Schuster DM, Votaw, JR, Nieh PT, Yu W, Nye JA, Master V, Bowman , F D, Issa MM, Goodman MM. Initial Experience with the Radiotracer Anti-1-Amino-3-18F-Fluorocyclobutane-1-Carboxylic Acid with PET/CT in Prostate Carcinoma. J Nucl Med 2007. 48:11a-12a.

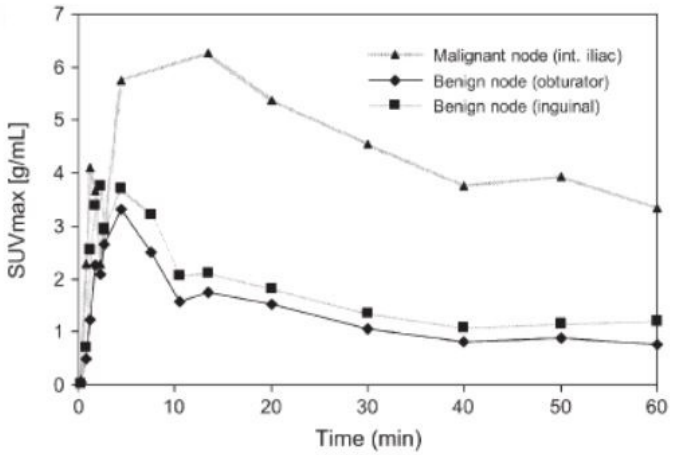


Figure 8: Time–activity curve compares uptake in a right internal iliac malignant node (14 x 11 mm) with benign right inguinal and right obturator (7 x 18 mm) node[Error! Bookmark not defined.]

Radiation Dosimetry

The radiation dosimetry values across all reported and published studies are compared in Table 17. Akhurst only reports the mean absorbed dose for the critical organ, liver, which was 0.0034 cGy/MBq (34 microGy/MBq)[14]. This value is in good agreement with the liver absorbed dose values in Table 17. The dosimetry values from study GE-148-001 were calculated from human biodistribution data using OLINDA/EXM (Organ Level Internal Dose Assessment/Exponential Modeling) software. The MIRD methodology was used to calculate the dosimetry and the method of ICRP Publication 60 to calculate the effective dose. The results were discussed against other results by J.A. Nye et al. (J Nucl Med 2007; 48:1017-20), Y. Asano et al. (Ann Nucl Med 2001; 25:414-418) and T. Akhursat et al. (J Nucl Med 2006; 47(Supp 1):492P) as well as the generic model of ICRP Publication 106 for ^{18}F-labelled amino acids.

[14] Akhurst T, Beattie B, Gogiberidze G, Montiel J, Cai, S, Lassman A et al. [18F]FACBC imaging of recurrent gliomas: a comparison with [11C]methionine and MRI. J Nucl Med, 47 (Suppl), 2006. 79P.

Table 17: Comparison of radiation dosimetry across studies

Target Region N Target activity	Mean Absorbed Dose per Unit Administered Activity (microGy/MBq) GE-148-001 3M, 3F HV 150 MBq	 NMK36-P1 6M HV 185 MBq	 Nye, 2007 3M, 3F HV 370 MBq
Adrenals	16.3	14.0	14.8
Brain	8.7	6.2	8.2
Breasts	13.7	-	4.4
Gallbladder Wall	16.7	16.9	17.8
Lower Large Intestine Wall	12.5	10.5	10.9
Small Intestine Wall	13.1	9.8	11.4
Stomach Wall	14.0	10.6	13.0
Upper Large Intestine Wall	13.0	10.4	11.8
Heart Wall	51.6	23.9	22.3
Kidneys	13.7	19.1	22.1
Liver	33.5	40.6	52.2
Lungs	34.5	17.9	11.7
Muscle	10.6	24.8	14.7
Ovaries	13.3	-	11.6
Pancreas	102.6	30.8	31.5
Red Marrow	24.7	16.1	15.4
Osteogenic Cells/bone	23.2	13.5	12.9
Skin	8.0	6.6	7.0
Spleen	23.8	21.3	20.2
Testes	17.2	14.5	8.6
Thymus	12.5	6.9	10.0
Thyroid	10.3	9.2	9.4
Urinary Bladder Wall	25.2	14.5	11.9
Uterus	46.3	-	11.5
Total Body	12.6	-	12.8
Effective dose (microSv/MBq)	22.2	13.8	14.1

The adult effective dose resulting from the administration of the recommended activity of 370 MBq of fluciclovine (^{18}F) is 8.2 mSv. For an administered activity of 370 MBq the typical radiation doses to the critical organs, pancreas, the cardiac wall and uterine wall are 37.8 mGy, 19.1 mGy and 16.5 mGy, respectively.

The mean effective dose per unit administered activity is 22 microSv/MBq (range: 20 to 26). The critical organ (i.e., the organ with the highest absorbed dose per unit administered activity) is the pancreas, with a mean absorbed dose of 102 microGy/MBq (range: 57 to 141).

Elimination

In Study GE-148-001, a mean of 3.2% of activity was excreted in the urine in over the collection period (mean 4.2 hours). Study NMK36-P1 continued collection for 24 hours, over which time a mean of 5.4% of activity was excreted in the urine. Washout of activity from most organs and tissues (with the exception of the pancreas) is slow. Washout of ^{18}F activity from the blood is such that about half of the maximum ^{18}F concentration in blood is reached by about 1 hour after administration.

Fluciclovine is not incorporated into proteins. Fluciclovine is not metabolised *in vivo*.

Special populations

The applicant did not submit studies in special populations.

The European Medicines Agency has deferred the obligation to submit the results of studies with Axumin in one or more subsets of the paediatric population in diagnosis of amino acid metabolism in solid tumours (see section 4.2 for information on paediatric use).

Fluciclovine (^{18}F) is not indicated for use in women (SmPC section 4.6).

No studies on fertility have been performed (smPC section 4.6).

Pharmacokinetic interaction studies

No interaction studies have been performed.

The impact of anti-mitotic agents and colony stimulating factors on uptake of fluciclovine in patients with prostate cancer has not been studied (SmPC section 4.5).

Pharmacokinetics using human biomaterials

No pharmacokinetics using human biomaterials studies were submitted (see discussion in pharmacology).

2.4.3. Pharmacodynamics

Mechanism of action

The applicant did not submit studies in humans to elucidate the mechanism of action of fluciclovine (^{18}F) (see discussion in pharmacology).

Primary and Secondary pharmacology

The applicant did not submit studies on primary and secondary pharmacology. Distribution of fluciclovine (^{18}F) was studied in healthy volunteers and biopsy-proven newly diagnosed prostate cancer in GE-148-001, and in suspected recurrent patients in Schuster 2007.

2.4.4. Discussion on clinical pharmacology

The effective half-life of fluciclovine equates to the radioactive half-life of ^{18}F, which is approximately 110 minutes. At the low chemical concentrations of 2 to 10 µg to be administered, fluciclovine (^{18}F) does not have any detectable pharmacological activity. The biodistribution was studied and fluciclovine (^{18}F) was found to be rapidly and extensively distributed to major organs and tissues with uptake being highest in organs with high levels of amino acid uptake, particularly liver, pancreas, bone marrow and skeletal muscle. The critical organ (i.e., the organ with the highest absorbed dose per unit administered activity) was the pancreas. Washout of activity from most organs and tissues (with the exception of the pancreas) is slow.

Fluciclovine is not metabolised *in vivo*. The major route of elimination is via the renal pathway. Urinary excretion is slow, reaching approximately 3% of administered radioactivity within 4 hours and 5% within 24 hours.

Distribution of fluciclovine (^{18}F) was studied in 6 HVs and 6 patients with biopsy-proven newly diagnosed prostate cancer after administration of 150 MBq, and in suspected recurrent patients. In healthy volunteers the organs with the highest initial uptake was clarified: liver, red bone marrow, lung and pancreas. In patients with newly diagnosed prostate cancer the uptake was rapid and it was high in tumour, lymph node lesions and vesicle lesions. In patients with suspected recurrence, uptake was rapid in local lesions.

The biodistribution data (organ uptake) has been included in the SmPC in section 5.2. Fluciclovine (^{18}F) accumulates in prostate cancer and other types of cancer but also in normal tissues and some other prostate pathologies (such as benign prostatic hyperplasia, chronic prostatitis, high grade prostatic intraepithelial hyperplasia). In addition, fluciclovine uptake may be increased by an inflammatory reaction to recent radiotherapy or cryotherapy.

Fluciclovine (^{18}F) is preferentially taken up into prostate cancer cells compared with surrounding normal tissues. Uptake by tumours is rapid, with the highest tumour-to-normal tissue contrast between 4 and 10 minutes after injection and continuing for around 30 minutes, with a 61% reduction in mean tumour uptake at 90 minutes after injection.

Washout of activity from most organs and tissues (with the exception of the pancreas) is slow. Activity in the brain is low. With increasing time post injection, distributed uptake is apparent and is mostly associated with skeletal muscle. Washout of ^{18}F activity from the blood is such that about half of the maximum ^{18}F concentration in blood is reached by about 1 hour after administration.

No data on primary pharmacology of fluciclovine (^{18}F) has been provided in humans with benign prostatic hyperplasia, chronic prostatitis or high grade prostatic intraepithelial hyperplasia). This is of concern as in vivo fluciclovine (^{18}F) PET imaging will presumably be tracing the fluciclovine (^{18}F) influx into tumours as well as some other pathologies such as benign prostatic hyperplasia, chronic prostatitis or high grade prostatic intraepithelial hyperplasia. There is a warning in section 4.4 of the SmPC that fluciclovine (18F) uptake is not specific for prostate cancer and may occur with other types of cancer, prostatitis and benign prostatic hyperplasia. False-positive cases have been also described in association with an inflammatory response after cryotherapy and radiation artefacts in patients previously treated with radiotherapy. Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, should be considered where appropriate.

The dosimetry data from Study GE-148-001 was regarded as the most comprehensive assessment of the radiation dosimetry of fluciclovine (^{18}F) and these data are described in the SmPC in section 11.

No pharmacodynamic studies or data on secondary pharmacology were submitted. This is acceptable as the administered dose is below the limits of detection in the plasma and hence, no pharmacological activity is expected from this low concentration level. At the chemical concentrations used for diagnostic examinations, fluciclovine (^{18}F) does not appear to have any pharmacodynamic activity.

The impact of quantitative/semiquantitative measurement of fluciclovine (^{18}F) uptake as an aid to image interpretation has not been assessed. A quantitative correlation between fluciclovine uptake and enhanced fluciclovine influx into cells was not assessed *in vivo* in healthy volunteers or prostate cancer patients.

The recommendation of at least 4 hour fasting was discussed. The applicant did not submit a study demonstrating food effect on the distribution and updtake of fluciclovine as well as bladder activity in patients

that have hydrated before the procedure. However, taking into account the literature and the current clinical practice with similar products, a period of fasting is usually recommended before injection. It was determined that 4 hours of fasting was sufficient to get a low level of amino acids in the plasma in order to prevent any possible interference with the uptake of the active substance. To avoid significant bladder activity, it is recommended that patients fast for at least 4 hours prior to the scan, drinking only sips of water within 4 hours prior to the scan (SmPC section 4.2)

No interaction studies have been performed. In *in vitro* studies, fluciclovine (^{18}F) was not taken up by common drug transporters indicating a negligible potential for drug interactions. Therefore, no relevant interactions between fluciclovine and other drugs are expected.

It has been reported that registered fluorocholine (^{18}F) products in the EU that fluorocholine (^{18}F) uptake is influenced by antiandrogen therapy, antimitotic drugs and colchicine and colony stimulating factors (G-CSF or erythropoietin). The impact of anti-mitotic agents and colony stimulating factors on uptake of fluciclovine in patients with prostate cancer has not been studied.

The pharmacokinetics in patients with renal or hepatic impairment have not been characterised (SmPC section 4.2, 4.4 and 5.2). Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients. Therefore, this has been included in the RMP as missing information.

No differences considered to be of likely clinical significance were noted between males and females. It is noted that the claimed indication is intended to be used in males only.

An analysis of the potential impact of variations in body mass did not show substantial changes in the effective radiation dose for the standard injected dose of 370 MBq. Therefore, no dose adjustments based on weight were recommended. The proposed dose is a fixed dose.

No dose adjustment requirements for the elderly population.

There is no relevant use of fluciclovine (^{18}F) in children and adolescents for the indication of prostate cancer.

Fluciclovine (^{18}F) is intended as a single use injection. Dynamic imaging assessment demonstrates persistence of imaging uptake in malignant tissue for up to 40 minutes post injection. After 90 minutes, efflux of fluciclovine from soft tissue (particularly lymph node lesions) results in tumour uptake appearing similar to background. For this reason early image acquisition starting rapidly following initial injection is recommended. The patient should be positioned supine with arms above the head. A CT scan should be obtained for attenuation correction and anatomic correlation. PET scanning should begin from 3-5 minutes (target 4 minutes) after completion of the injection; an acquisition time of 3 minutes per bed position is recommended. Increasing the duration of acquisition over the pelvis may increase the sensitivity of detection of disease. It is recommended that image acquisition should start from mid-thigh and proceed to the base of the skull. Typical total scan time is between 20-30 minutes.

For method of preparation, see section 12 of the SmPC.

The use of either intravenous iodinated CT contrast or oral contrast media is not required to interpret fluciclovine (^{18}F) PET images.

Method of administration

Axumin is for intravenous use.

The activity of fluciclovine (^{18}F) has to be measured with an activimeter immediately prior to injection.

Axumin should be administered as a bolus intravenous injection. The recommended maximum volume of injection of undiluted Axumin is 5 mL. Axumin may be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection by a factor of 8. The injection should be followed by an intravenous flush of sterile sodium chloride 9 mg/ml (0.9%) solution for injection to ensure full delivery of the dose.

Axumin is for multidose use.

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

For patient preparation, see section 4.4.
Following strenuous exercise the rates of protein synthesis and degradation and of amino acid transport are increased and there is a theoretical risk of an increase in uptake of fluciclovine to those muscles that have been exercised.Therefore, it should be recommended to the patient that they do not undertake any significant exercise for at least a day before the fluciclovine (^{18}F) scan.

Elderly
No dose adjustment required.

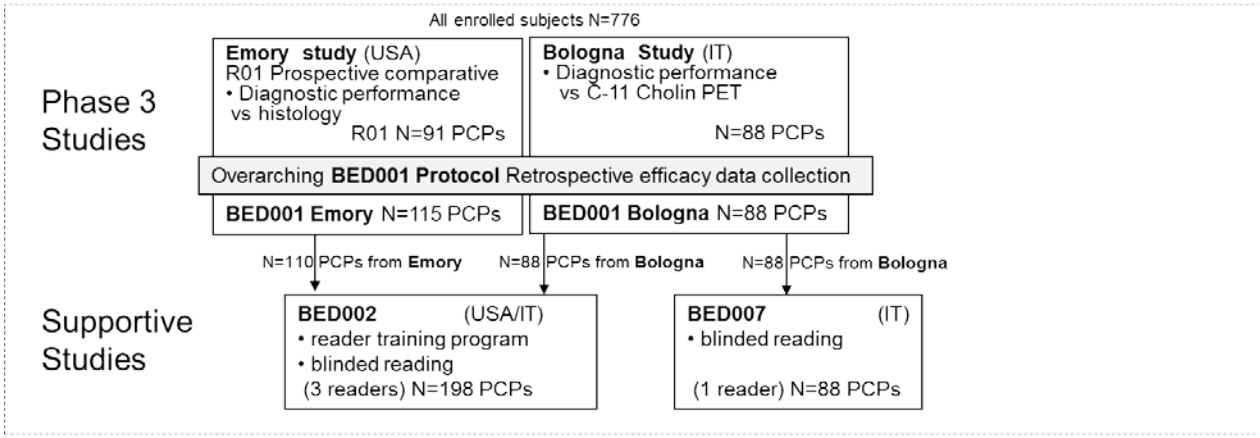
Paediatric population
There is no relevant use of fluciclovine (^{18}F) in the paediatric population.

2.4.5. Conclusions on clinical pharmacology

The PK of fluciclovine (^{18}F) was characterised in several Phase I studies measuring biodistribution and dosimetry. The mechanism of action and PK data for fluciclovine (^{18}F) has been adequately described in the SmPC (Section 5.1 and 5.2) and information on the potential in vivo pharmacodynamic drug-drug interactions with a number of compounds that may be frequently used by the intended population was also included in the SmPC section 4.5.

The CHMP considers that the clinical pharmacology of fluciclovine has been adequately described and no further studies are necessary.

2.5. Clinical efficacy



PCPs= Prostata Cancer Patients

2.5.1. Dose response study(ies)

No clinical studies on the optimal dose, optimal method of administration and optimal timing for image acquisition have been submitted.

The recommended activity of fluciclovine (^{18}F) to be administered in adults (i.e. 370 MBq) is based on the evaluation of imaging quality and dosimetry which has been performed mostly at doses of 370 MBq. Clinical experience in Norway where lower doses were used (<300 MBq) suggested that lowering the dose administered may have a deleterious effect on image quality. This application is based on retrospective assessment of data collected at different sites. Each site used different approaches to image acquisition, based on standards of practice in the individual unit. Based on information from blinded evaluation of images from two of the sites it seems that images acquired using shorter image acquisition time per bed position results in low count images which may be difficult to interpret; similar findings have been noted, for fludeoxyglucose (^{18}F)[15,16] .

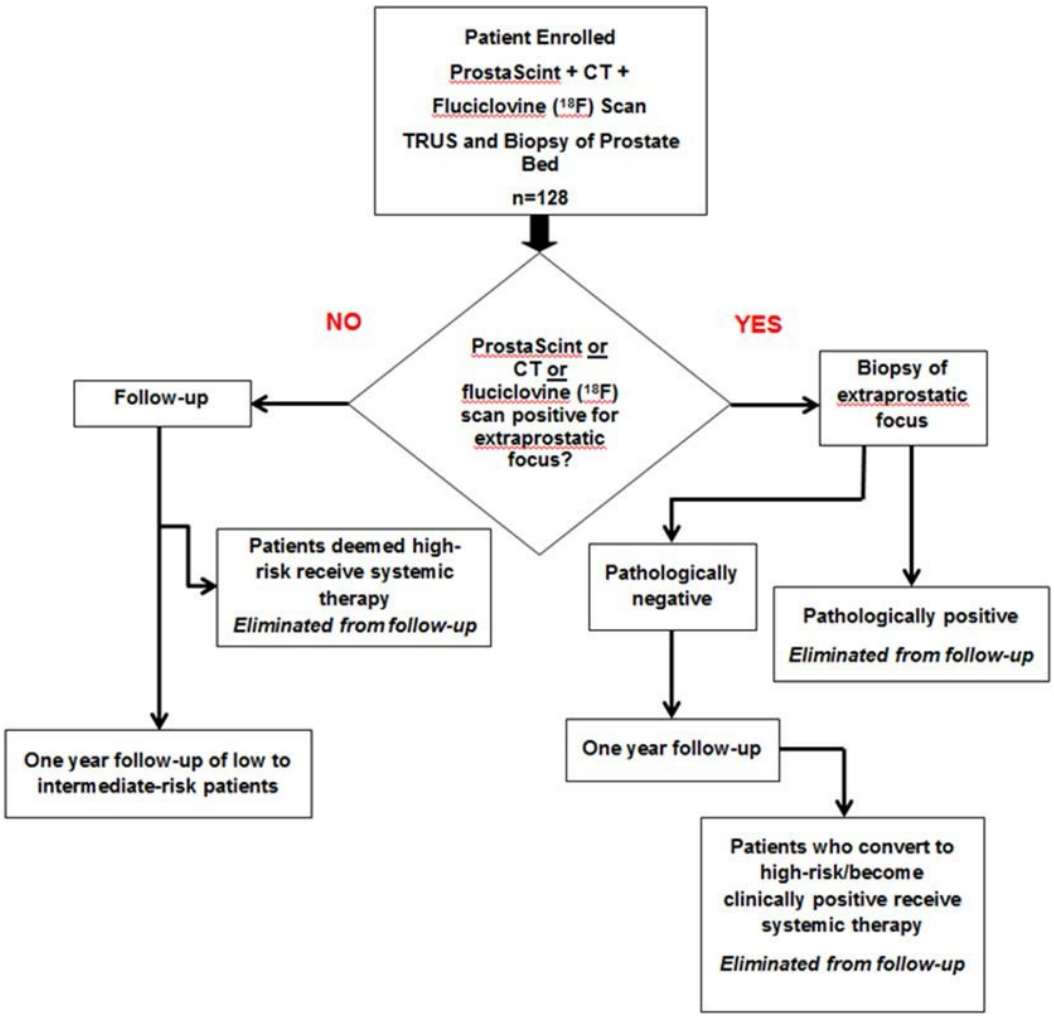
2.5.2. Main study(ies)

Study 1 BED001 Emory: A Retrospective Observational Study investigating the Safety and Effectiveness of Fluciclovine (^{18}F) PET in Human Subjects

BED001 was a retrospective observational study designed to collect, pool and analyse relevant data collected from multiple research sites including Emory University. Therefore BED001 Emory is the part of BED001 study concerning data from the Emory study.

[15] Komar G, Teras M, Seppa M, Hirvonena J, Vahlkverg T, Bergmand J, Minn H. Comparison of 2D and 3D performance for FDG PET with different acquisition times in oncological patients. Nic Med Comm 2009; 30: 16-24.
[16] Brown C, Dempsey M-F, Gillen G and Elliott AT. Investigation of 18F FDG 3D mode PET image quality and acquisition time. Nuc Med Comm 2010; 31: 254-9.

Emory study: Fluciclovine (^{18}F) PET-CT for the Detection and Staging of Recurrent Prostate Carcinoma[17]



Methods

Study Participants

Inclusion Criteria

- Eighteen years of age or older
- Originally diagnosed with localized (Stage T1c, T2, or T3) prostate carcinoma and having undergone what was considered definitive therapy for localised disease
    - In the case of brachytherapy, cryotherapy, or external beam radiation, treatment had occurred at least 2 years in the past

[17] Schuster DM, Nieh PT, Jani AB, Amzat R, DuBois Bowman F, Halkar RK, Master VA, Nye JA, Odewole OA, Osunkoya AO, Savir-Baruch B, Alaei-Taleghani P, Goodman MM. Anti-3-[18F]FACBC positron emission tomography-computerized tomography and 111In-capromab- pendetide single photon emission computerized tomography-computerized tomography in recurrent prostate carcinoma: Results of a prospective clinical trial. J Urol 2014; 191: 1446-53

- Had a suspicion of recurrent prostate carcinoma as defined by ASTRO criteria:
    - Three consecutive rises of PSA or earlier, if clinically appropriate
    - And/or nadir + 2.0 after radiotherapy
    - And/or >0.3 after prostatectomy
- Ability to lie still for PET scanning
- Ability to provide written informed consent

Exclusion Criteria

- Less than 18 years of age
- Historic disease staging of greater than T3
- Less than 2 years since brachytherapy, cryotherapy, or external beam radiation therapy
- Absence of suspicious PSA elevation
- Inability to lie still for PET scanning
- Inability to provide written informed consent
- Whole-body bone scintigraphy findings characteristic of metastatic prostate carcinoma
- Less than 2 months since any prior prostate biopsy

Treatments

Subjects had previously undergone conventional prostate cancer staging, according to institutional guidelines, including bone, ProstaScint and pelvic CT scanning and trans-rectal ultrasound (TRUS), where appropriate. Subjects were screened within 21 days prior to the fluciclovine (^{18}F) PET scanning procedure (Day 1). All suspicious extraprostatic findings were confirmed by biopsy at least 24 hours after imaging. Subjects were followed up for one year, regardless of the initial findings, in order to optimise the correlation of imaging to clinical findings.

- Fluciclovine (^{18}F) PET-CT scanning occurred after an IV bolus of 370 MBq.

The fluciclovine (^{18}F) PET-CT imaging protocol used, and based on the investigator's previous experience with the radiotracer, assumed tracer uptake was most intense during the 45 minutes after injection. PET-CT scanning of the abdominopelvic region was initiated 3 minutes after completion of the fluciclovine (^{18}F) injection to allow for blood pool clearance.

Scanning was done on a Discovery DLS or 690 PET-CT scanner (GE Healthcare, Milwaukee, Wisconsin) with 5–16 minute (early), 17–28 minute (delayed) and 29–40 minute (delayed 2) acquisitions.

Eligible subjects underwent fluciclovine (^{18}F) PET-CT scanning on Study Day 1, as outlined below:

- All subjects fasted for four hours to normalize their neutral amino acid levels. One hour prior to scanning, the subjects drank 500 mL of 1.2% (Readi-Cat) oral contrast over 1 hour to maximize conspicuity of abdomen and pelvic structures
- Prior to placement in the tomographic gantry, an IV catheter was placed for injection of tracer
- The subject was placed in the tomographic gantry for a CT scan of the chest-abdomen-pelvis (80-120 mA) to be utilized for anatomic imaging and correction of emission data (approximately 1 minute)
- A bolus of fluciclovine (^{18}F), approximately 10.0 mCi (3.70 x 108 Bq), was administered IV over 1-2 minutes
- At four minutes, a 4 minute per bed position PET acquisition commenced at the pelvis (to include the entire prostate or prostate bed)
- Three bed positions were obtained covering the pelvis through abdomen to above the kidneys

- This sequence was repeated twice

In the proposed SmPC the applicant states that the patient should be positioned supine with arms above the head. A CT scan should be obtained for attenuation correction and anatomic correlation. PET scanning should begin from 3-5 minutes (target 4 minutes) after completion of the injection; an acquisition time of 3 minutes per bed position was recommended. It is recommended that image acquisition should start from mid-thigh and proceed to the base of the skull. Typical total scan time is between 20-30 minutes. Increasing the duration of acquisition over the pelvis may increase the sensitivity of detection of disease.

- Histopathological sampling:

Subjects who had undergone prior prostatectomy underwent TRUS and anastomotic site biopsy

Subjects who had undergone previous brachytherapy or external beam radiation therapy underwent standard TRUS 12-core biopsy

- Recording of PSA levels until at least 12 months after the last administration of fluciclovine (^{18}F)

- PET-CT scanning was to be suspended in any subject who experienced a Grade 3 or greater toxicity, per NCI (National Cancer Institute) Common Toxicity Criteria for Adverse Event (CTCAE) Reporting Version 3.0, with a causality attribution of probably or definitely associated with fluciclovine (^{18}F). Fluciclovine (^{18}F) PET-CT scanning was only to be resumed once the toxicity resolved to Grade 1 or below.

Objectives

Primary:

- To investigate the ability of fluciclovine (^{18}F) PET- Computed Tomography (CT) imaging to detect recurrence of prostate carcinoma in the prostate bed validated by pathologic analysis of prostate bed biopsies and patient follow up.

Secondary:

- To investigate the ability of fluciclovine (^{18}F) PET-CT imaging to detect extra-prostatic recurrence of prostate carcinoma validated by pathologic analysis of suspect lymph nodes sampled via percutaneous and laparoscopic methods and patient follow up.
- To evaluate the ability of fluciclovine (^{18}F) PET-CT imaging in the discrimination of local recurrence of prostate carcinoma from that of extra-prostatic recurrence validated by a combination of pathologic analysis, one-year follow up imaging and clinical correlation

Outcomes / endpoints

The primary endpoint was positive predictive value (PPV) of fluciclovine (^{18}F) PET-CT scan at lesion level versus the SOT (histological verification).

The secondary endpoints were:

- PPV at region level (regions 1-4) and patient level vs SOT.

- NPV, sensitivity, specificity detection rate (DR) of fluciclovine (18F) PET-CT scan vs SOT. All of them at lesion level, region level (regions 1-4) and patient level.
- PPV, NPV, sensitivity, specificity detection rate (DR) of fluciclovine (18F) PET-CT scan vs reference standard based on a composite of histological verification &/or findings of at least 1 other imaging modality (≤ 3 months prior to and ≤ 6 months after fluciclovine (^{18}F) scan) &/or post-therapy PSA levels. Analyses were conducted as outline above and outcomes presented separately at Region (Regions 1 – 4) and Subject level.
- Agreement and disagreement between fluciclovine (^{18}F) and the other imaging findings. Analyses were presented separately for each imaging modality and conducted at Region level only.
- The DR of fluciclovine (^{18}F) imaging was presented at Region level (Regions 1 – 3 and 5 – 8) and Subject level.
- Sub-group analysis including age, weight, race, prior and concurrent anti-cancer therapy, Gleason Score of primary tumour, D'Amico risk score of primary tumour and PSA (value at time of scan, doubling time and velocity) were performed where available data permitted.

The interpretation of fluciclovine (^{18}F) PET-CT was visual. A region in the prostate was considered positive by fluciclovine (^{18}F) scan if there was asymmetric focal activity exceeding prostate background activity according to the criteria utilized by Yamaguchi (2005) during the investigation of choline (^{11}C) PET uptake in the prostate. If a prostatectomy had been conducted, abnormal focal uptake over background was considered positive.

A lymph node was to be considered visually positive if there was abnormal activity over expected soft tissue and/or blood pool. Intensity was recorded as follows:

- Mild: above blood pool but less than muscle
- Moderate: above muscle but less than marrow
- Intense: above marrow

Lesion and Region level locations were defined as presented in Table 18:

Table 18: Definition of Lesion and Region Levels used for Analysis of BED-001 Primary and Secondary Effectiveness Endpoints

Lesion			
Prostate and prostate bed	Lymph nodes above diaphragm	Lymph nodes below diaphragm	Bones - skull
Bones – neck and chest	Bones below diaphragm	Soft tissue/parenchymal	
Region			
Region 1: Prostate and prostate bed	Region 2: Pelvic lymph nodes	Region 3: Other nodal, bone or soft tissue (including all other lesion locations)	Region 4: Extra-prostatic (including Region 2 & Region 3 locations)

Only areas with assessed positive fluciclovine (^{18}F) uptake were biopsied at Emory University. No systematic histological assessment of negative either lymph node areas or extraprostatic sites reported on the scan were performed. In an attempt to correct this additionally a reference standard was applied and a scan was considered a true positive if findings were confirmed by a fall in PSA values following intervention which would have included the site of a positive finding on PET-CT, or corroborative findings on other image modalities within 3 months prior and 6 months after the fluciclovine (^{18}F) scan. A true negative was assessed as negative histopathology on biopsy of negative lesions, stable PSA values without specific treatment, or continued negative findings on other image modalities within 6 months of the fluciclovine (^{18}F) scan.

Sample size

The planned sample size was 128 scans based on power analyses for testing hypotheses that compared an accuracy measure to a specified value and assuming a 5% type-I error rate. Sensitivity and specificity measurements for fluciclovine (^{18}F) that exceeded 0.9 were anticipated, with the power to detect improvement over baseline levels of 0.8, i.e. reflecting at least a 12.5% improvement. To detect effect sizes corresponding to the aforementioned levels, it was determined that the proposed sample size of 128 would provide the minimum power of 0.94 with observed fluciclovine (^{18}F) sensitivity and specificity exceeding 0.9. Power analyses were also conducted assuming 15% missing data and resulted in a targeted sample size of 109. The reduced sample size of 109 subjects would provide power of >0.90 for sensitivity/specificity exceeding 0.9.

Randomisation

This study was not randomised.

Blinding (masking)

This study was unblinded. However, interpretation of fluciclovine (^{18}F) scans in the original study R01 was performed in a blinded manner at least to the result of both the other imaging tests and histopathology.

Statistical methods

For all primary (positive predictive value (PPV)) and secondary (negative predictive value (NPV), sensitivity, specificity detection rate (DR)) analyses, the point estimates (expressed in percentages) and the 2-sided 95% exact confidence interval, calculated using the method of Clopper & Pearson, 1934 were presented. Analyses were conducted at Lesion, Region and Subject level, where applicable. At the Lesion level a subject was counted as many times as he had lesions. At the Region level, each subject was counted for each region where a lesion was detected, regions being analysed separately. For the primary effectiveness analysis and each of the secondary effectiveness endpoints, fluciclovine (^{18}F) imaging findings at Lesion level were cross tabulated with biopsy findings as SOT. The number of lesions biopsied in the analysis (N) and the number (and %) meeting each of the following criteria were presented:

- True positive (TP)
- False positive (FP)
- True negative (TN)

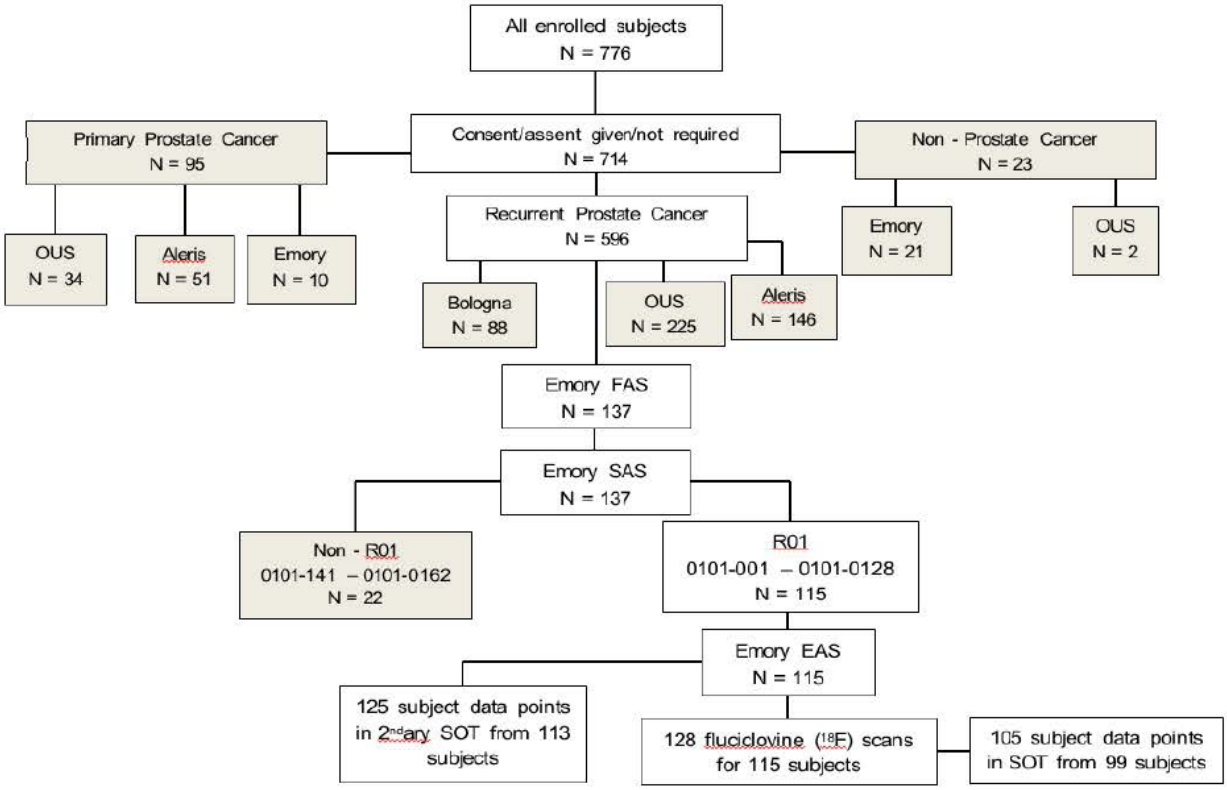
• False negative (FN)

Point estimates (expressed in %), the 2-sided 95% exact confidence interval and p-value were presented for each endpoint. These analyses were also conducted at Region level (Regions 1 – 4) and Subject level, and presented separately. Fluciclovine (^{18}F) imaging findings (region, anatomical location, fluciclovine (^{18}F) finding) were listed. Details of the findings (including region, anatomical location, fluciclovine (^{18}F) finding, biopsy finding) were listed for fluciclovine (^{18}F) imaging and for biopsy.No formal interim data analyses were pre-planned.

The statistical significance of differences in sensitivity, specificity and overall accuracy between fluciclovine PET-CT and Prostascint imaging was calculated using the McNemar chi- square test, which adjusts for correlations in the accuracy measures for each patient. The statistical significance of differences in PPV and NPV was assessed using approximate tests based on the difference between 2 proportions. Statistical significance was determined using a type I error rate of a ¼ 0.05.

Results

Participant flow



Recruitment

The **BED-001** study retrospectively collected data from centres in the US (Emory), Italy (Bologna) and Norway (Oslo). The study was initiated in November 2007 and was completed in July 2012.

Conduct of the study

Six amendments have been made to the study protocol (Table 19), with the exception of one minor change that refers to the data collection period definitions or modalities for data collection at different sites. The study design was based on retrospective datasets.

Table 19: Summary of the Substantial Changes made to the R01 Study Protocol

Date	Summary of Changes
14 Nov 2007	Change to inclusion criterion 4: clarification of prior therapy; definition of suspected recurrence
29 Jul 2008	Allowing subjects who were negative on the initial fluciclovine (^{18}F) PET-CT scan, but present with rising PSA to have another scan, subject to inclusion criteria
18 Nov 2008	Clarification of type of and schedule for laboratory tests and vital signs: CBC, complete metabolic profile and urinalysis to be performed on the morning of the scan and 1 week after; vital signs (temperature, pulse, respiration rate, blood pressure) prior to fluciclovine (^{18}F) infusion and every 15 minutes during infusion
05 Nov 2010	Addition of urinalysis immediately following the scan
23 Feb 2012	Increase period of post-scan follow-up from 1 to 5 years
13 Sep 2012	Inclusion of Data and Safety Monitoring Plan

Baseline data

Table 20: Subject Demography and Baseline Characteristics for Recurrent Prostate Cancer Subjects at the Emory Site (including R01)

Number of subjects in FAS (N)	**137**		**115**
Study	**Emory (BED-001)**		**R01**
Age n (%)	**137**	**(100)**	**115**
Mean ± SD	66.6	7.77	NC
Median (range)	67.0+	(42, 90)	NC
Race n (%)			
Black or African American, Asian, Other	28	(20)	22
White	98	(71.5)	83
Missing	11	(8.0)	10
PSA (ng/mL) n[1]	**125**		NC
Mean ± SD	5.961	7.5571	NC
Median (range)	2.920	(0.05, 44.76)	NC
Recurrent PCa therapy n (%)	**131**	**(95.6)**	**115**
Radical prostatectomy only	19	(13.9)	15
Radical prostatectomy + others	5	(3.6)	4
Radiotherapy only	40	(29.2)	16

Radiotherapy + others	52	(38.0)	42
Others	15	(10.9)	38
Gleason score n (%)	**92**	**(67.2)**	**84**
≤6	38	(41.3)	36
7	39	(42.4)	35
8-10	15	(16.3)	13
D'Amico classification n (%)	**137**	**(100)**	**64**
Low risk	6	(4.4)	6
Intermediate risk	40	(29.2)	37
High risk	30	(21.9)	21
Indeterminate	61	(44.5)	51
Subjects having a fluciclovine (^{18}F) PET-CT scan	**137**		**115**
Total number of fluciclovine PET-CT scans	**149**		**128**

Abbreviation(s): N = the number of subjects in the analysis set; n = the number of subjects meeting the criterion; % = subjects/N*100; FAS = full analysis set; NC = not calculated

[1]Baseline defined as last value prior to fluciclovine (^{18}F) administration

Numbers analysed

Data from all 115 (100%) subjects were included in the FAS, and EAS analysis sets.

Ninety nine (99) of these 115 subjects had a histopathology report available for biospies/surgical specimens/ cytological evaluations performed on lesions scanned by fluciclovine (^{18}F) PET-CT imaging. Seven (7) of these subjects had imaging and histopathology data available from two fluciclovine (^{18}F) PET-CT scanning time points. For one (1) of the fluciclovine (^{18}F) PET-CT scan images the on-site reader was unable to make a definite allocation of positive or negative for a lesion in which there was a degree of fluciclovine (^{18}F) uptake, at a level similar to background. Consequently this lesion was declared indeterminate and 105 subject data points feature in the primary SOT analysis.

Data from other imaging modalities conducted within 6 months of the fluciclovine (^{18}F) PET-CT scan and/ or PSA values were available for a further 14 subjects, twelve (12) of whom had data available from two fluciclovine (^{18}F) PET-CT scanning time points. Consequently 125 subject data points feature in the reference standard analysis.

Outcomes and estimation

The pivotal efficacy data derives from 115 patients recruited into the BED-001 study at Emory University. Patients were adult and elderly men presenting with suspected recurrence, based on elevated blood PSA levels after primary curative treatment of localized prostate cancer and with negative bone scintigraphy. Patients with non-surgical therapy were treated at least 2 years before. Fluciclovine ^{18}F PET-CT was restricted to the abdomino-pelvic region.

Histopathology standard of truth data was available for 99 of the 115 subjects. Histological assessment of extraprostatic sites (either regional lymph nodes or distant sites) was only conducted for sites with positive image findings.

The PPV of fluciclovine (^{18}F) PET-CT, using biopsy as SOT, significantly exceeded 50% at Lesion, Region and Subject level, exceeding 90% at Region 2 (95.8%) and Region 4 (93.1%), and was statistically significant in each case. Sensitivity exceeded 90% at Subject and Region level, was 100% for Regions 2 and 4, and was statistically significant at all levels ($p<0.0001$). Sensitivity analysis allocating indeterminate lesions as either positive or negative had no statistically significant bearing on the results. NPV was 80.4% at Lesion level and 92.3% at both Subject level and Region level (Region 1). Specificity exceeded 50% at Lesion level and was 38.7% at Subject level. No data are presented for NPV and specificity for Regions 2 and 4 since the number of subjects with negative standard of truth was insufficient to support these analyses. The DR exceeded 80% at Subject level.

Table 21: Diagnostic performance of fluciclovine (^{18}F) PET-CT vs Histopathology in Subjects with Recurrent Prostate Cancer in Study R01 (Emory)

	Subject	Lesion	Region		
			Prostate & Prostate bed (R1)	Pelvic lymph nodes (R2)	Extra-prostatic (pelvic lymph nodes, other noes, bone and soft tissue) (R4)
N	105	371	97	24	29
True Positive n (%)	73 (69.5)	126 (34.0)	57 (58.8)	23 (95.8)	27 (93.1)
False Positive n (%)	19 (18.1)	82 (22.1)	27 (27.8)	1 (4.2)	2 (6.9)
True Negative n (%)	12 (11.4)	131 (35.3)	12 (12.4)	0 (0.0)	0 (0.0)
False Negative n (%)	1 (1.0)	32 (8.6)	1 (1.0)	0 (0.0)	0 (0.0)
PPV n (%) [95% CI] p-value	73/92 (79.3) [69.6, 87.1] <0.0001	126/208 (60.6) [53.6, 67.3] 0.0014	57/84 (67.9) [56.8, 77.6] 0.0007	23/24 (95.8) [78.9, 99.9] <0.0001	27/29 (93.1) [77.2, 99.2] <0.0001
NPV n (%) [95% CI] p-value	12/13 (92.3) [64.0, 99.8] 0.0017	131/163 (80.4) [73.4, 86.2] <0.0001	12/13 (92.3) [64.0, 99.8] 0.0017	0/0 (0.0)	0/0 (0.0)

Sensitivity **n (%)** **[95% CI]** **p-value**	73/74 (98.6) [92.7, 100.0] <0.0001	126/158 (79.7) [72.6, 85.7] <0.0001	57/58 (98.3) [90.8, 100.0] <0.0001	23/23 (100.0) [85.2, 100.0] <0.0001	27/27 (100.0) [87.2, 100.0] <0.0001
Specificity **n (%)** **[95% CI]** **p-value**	12/31 (38.7) [21.8, 57.8] 0.8595	131/213 (61.5) [54.6, 68.1] 0.0005	12/39 (30.8) [17.0, 47.6] 0.9881	0/1 (0.0)	0/2 (0.0)
Detection Rate **n (%)** **[95% CI]** **p-value**	92/105 (87.6) [79.8, 93.2] <0.0001	208/371 (56.1) [50.8, 61.2] 0.0111	84/97 (86.6) [78.2, 92.7] <0.0001	24/24 (100.0) [85.0, 100.0] <0.0001	29/29 (100.0) [88.1, 100.0] <0.0001

Using the findings of other relevant imaging modalities, the PPV of fluciclovine (^{18}F) PET-CT scanning significantly exceeded 50% in Regions 1 – 3 in all but 1 instance. The lowest agreement was approximately 64% in Region 1 and the highest was 100% in Regions 2 and 3, for fluciclovine (^{18}F) PET-CT vs MRI in each instance. Agreement between fluciclovine (^{18}F) PET-CT and unenhanced CT scanning was 18% in Region 1 as detection of prostate lesions is poor following unenhanced CT.

Using the findings of other relevant imaging modalities and clinical follow-up as reference standard in the recruited population, patient-based sensitivity and specificity of fluciclovine (^{18}F) PET-CT for detection of prostate/prostate bed recurrences were 94.7% (89/94) (95%CI: 88.0-98.3%) and 54.8% (17/31) (95%CI:36-72.7%), respectively. For detection of extraprostatic recurrences (regional lymph node and/or distal metastases) sensitivity was 84.2% (32/38) (95%CI: 68.7-94%) and specificity was 89.7% (78/87) (95%CI: 81.3-95.2%), respectively.

Description of the false positive cases

False-positive and false-negative results of fluciclovine (^{18}F) PET-CT have been described. Twenty seven scans from 26 patients had false positive findings in the prostate/prostate bed region; 7 of these had true positive findings in additional areas and so count as true positive in the patient analysis, which is the reason for the apparent discrepancy between patient and region assessments. With the exception of one case who had a negative biopsy (fibrous tissue) reported and a case which had undergone PET-CT one month after cryotherapy (which may have resulted in inflammatory response and a false positive finding in the cryotherapied tissues), all of these patients had been previously treated with radiotherapy. Review of these cases indicates that the histopathology report shows 'radiation artefact'.

With respect to false negatives, only 1 patient had a completely negative scan subsequently demonstrated to be a false negative scan based on histopathological assessment; this patient, who had a PSA value of 0.28ng/mL, underwent a 6 core needle biopsy which demonstrated a tiny (<5% volume) area of adenocarcinoma within 1/6 samples taken; brachytherapy changes were noted in the remaining 5 core samples. The fluciclovine (^{18}F) scan was reported negative in the prostate and there was no evidence of metastatic spread (no extraprostatic sites were biopsied). The very small volume of tumour noted on the biopsy may have been below the critical size (~5mm) for reliable PET assessment in this case.

In the Emory subset, the PET scans showing distant metastases only involved distal lymph nodes, soft tissue and bone but not visceral metastases.

Ancillary analyses

Positive Likelihood Ratio and Negative Likelihood Ratio

As shown in Table 21, patient-based sensitivity and specificity for detection of recurrent prostate cancer, calculated in 99 patients with 105 fluciclovine (^{18}F) PET-CT scans at Emory University (where the bulk of the BED-001 study data were obtained) versus the standard of truth, were 98.6% (95%CI: 92.7-100%) and 38.7% (95%CI: 21.8-57.8%), respectively. These figures were obtained combining local and distant recurrences (intraprostatic, regional and non-regional lymphatic, bone and soft tissue sites). The calculated positive likelihood ratio was 1.61 (95%CI: 1.22-2.13) and negative likelihood ratio was 0.035 (95%CI: 0-0.26).

Summary of main study

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 22: Summary of Efficacy for trial BED 001 EMORY

Title: **18F-FACBC PET-CT for the Detection and Staging of Recurrent Prostate Carcinoma**			
Study identifier	CA129356-01/BED001 Emory		
Design	A phase III retrospective observational study investigating the safety and efficacy of Fluciclovine (18F) PET-CT in patients with suspected recurrent prostate carcinoma vs histopathology report from a biopsy or surgical specimen		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28 November 2007 – 10 July 2012 not applicable not applicable
Hypothesis	Superiority:		
Treatments groups	Fluciclovine (18F)		N=115 128 fluciclovine (^{18}F) scans for 115 subjects 105 subject data points in SOT from 99 subjects
Endpoints and definitions	Primary endpoint	Positive predictive value (PPV) %	True positive/(True Positive + False positive)
	Secondary endpoint	Negative predictive value (NPV) %	True negative/(True negative + False negative)
	Secondary endpoint	Sensitivity %	True positive/ (True positive + False negative)
	Secondary endpoint	Specificity %	True negative/ (True negative + False positive)
	Secondary endpoint	Detection rate	(True positive + False positive)/ data points in SOT
Results and Analysis			

Analysis description	**Primary Analysis**						
Analysis population and time point description	Fluciclovine (^{18}F) PET-CT using histopathology report as standard of truth at the subject level,lesion level and site level						
Descriptive statistics and estimate variability	**Treatment group**		**Subject**	**Lesions**	**Site**		
					Prostate & prostate bed	**Regional lymph nodes**	**Extra prostatic (disease outside the prostate bed including regional and distant recurrences)**
	Number of subject		105	371	97	24	29
	TP n (%)		73 (69.5)	126 (34.0)	57 (58.8)	23 (95.8)	27 (93.1)
	FP n (%)		19 (18.1)	82 (22.1)	27 (27.8)	1 (4.2)	2 (6.9)
	TN n (%)		12 (11.4)	131 (35.3)	12 (12.4)	0 (0.0)	0 (0.0)
	FN n (%)		1 (1.0)	32 (8.6)	1(1.0)	0 (0.0)	0 (0.0)
Effect estimate per comparison	Primary endpoint	**PPV**	**subject**	**lesion**	**Prostate & prostate bed**	**Regional lymph nodes**	**Extra prostatic (disease outside the prostate bed including regional and distant recurrences)**
		%	79.3	60.6	67.9	95.8	93.1
		95%CI	69.6, 87.1	53.6, 67.3	56.8, 77.6	78.9, 99.9	77.2, 99.2
		p-value	<0.0001	0.0014	0.0007	<0.0001	<0.0001
	Secondary endpoint	**NPV**					
		%	92.3	80.4	92.3	0	0
		95%CI	64.0, 99.8	73.4, 86.2	64.0, 99.8	-	-
		p-value	0.0017	<0.0001	0.0017	-	-
	Secondary	**Sensitivity**					

	endpoint	%	98.6	79.7	98.3	100	100
		95% CI	92.7, 100.0	72.6, 85.7	90.8, 100	85.2, 100	87.2, 100
		p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	Secondary endpoint	**Specificity**					
		%	38.7	61.5	30.8	0	0
		95%CI	21.8, 57.8	54.6, 68.1	17.0, 47.6	-	-
		p-value	0.8595	0.0005	0.9881	-	-
	Post-hoc analysis	**Positive likelihood ratio**	1.61	1.42	-	-	-
		95% CI	1.22, 2.13	1.15, 1.75	-	-	-
	Post-hoc analysis	**Negative likelihood ratio**	0.03	0.06	-	-	-
		95% CI	0, 0.26	0.01, 0.41	-	-	-
Notes	n/a						
Analysis description	**Secondary analysis**						
Using the findings of other relevant imaging modalities and clinical follow-up as reference standard instead of the standard of truth	Patient-based sensitivity and specificity of fluciclovine (18F) PET-CT for detection of prostate/prostate bed recurrences were 94.7% (89/94) (95%CI: 88.0-98.3%) and 54.8% (17/31) (95%CI:36-72.7%), respectively. For detection of extraprostatic recurrences (regional lymph node and/or distal metastases) sensitivity was 84.2% (32/38) (95%CI: 68.7-94%) and specificity was 89.7% (78/87) (95%CI: 81.3-95.2%)..						

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

The pivotal efficacy data derives from BED-001, a study which recruited 596 male subjects with recurrent prostate cancer from 4 clinical sites in three countries. A histopathology report from a biopsy or surgical specimen was available for 143 of the 596 subjects, 105 (73%) from Emory University, 12 (8.4%) from Bologna University and 26 (18%) from Oslo University Hospitals. Sites of metastases identified included prostate/prostate bed, seminal vesicles, regional/non-regional lymph nodes, soft tissues and bone.

The patient-based diagnostic performance of fluciclovine (^{18}F) versus the histopathology report to detect cancer prostate recurrence overall (at any location), and in 3 different locations (prostate/bed, regional lymph nodes, and distant metastases) is tabulated below (Table 23).

Table 23: Patient-based diagnostic performance of fluciclovine (18F) versus histopathology to detect cancer prostate recurrence overall (at any location), and in 3 different locations (prostate/bed, regional lymph nodes, and distant metastases) in study BED-001

Region	Overall	Local recurrence			Distal recurrence
		Biopsy of prostate/bed only	Biopsy of regional nodes	Total	
TOTAL	143	99	15	114	29
True positive	98	60	14	74	14
False positive	21	19	0	19	2
True negative	14	14	1	15	5
False negative	10	6	0	6	8
PPV*(95%CI)	82.4% (74.3; 88.7)	75.9 % (65.0;84.9)	100% (76.8;100)	79.6% (69.9;87.2)	87.5 % (61.7; 98.4)
NPV*(95%CI)	58.3% (36.6; 77.9)	70% (45.7;88.1)	100% (2.5;100)	71.4% (47.8;88.7)	38.5% (13.9; 68.4)
Sensitivity (95%CI)	90.7% (83.6, 95.5)	90.9% (81.3;96.6)	100% (76.8; 100)	92.5% (84.4;97.2)	63.6% (40.7;82.8)
Specificity (95%CI)	40% (23.9, 57.9)	42.4% (25.5;60.8)	100% (2.5;100)	44.1% (27.2;62.1)	71.4% (29.0;96.3)

*PPV – Positive Predictive Value; NPV - Negative Predictive Value

Supportive study(ies)

Study 2: BED-001 Bologna Study: ANTI-3-^{18}F-FACBC (anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid) in comparison to ^{11}C-choline PET/CT in the evaluation of subjects with suspected prostate cancer relapse

A Retrospective Observational Study investigating the Safety and Effectiveness of Fluciclovine (^{18F}) PET in Human Subjects.

Methods

Study Participants

Main Inclusion Criteria:

• Subjects with prostate cancer who have been treated with radical prostatectomy and/or radiotherapy at least three months prior to the baseline PET-CT scan

• Subjects with a clinically suspected relapse of the disease, in accordance with American Society of Radiology and Oncology (ASTRO) criteria (Roach, 2006):

  o Three consecutive PSA increases, or

  o PSA increase of at least 2.0 mg/mL above the nadir level following radiotherapy, and/or

  o Absolute PSA level of 0.3 mg/mL or more after prostatectomy

• Subjects who had already undergone conventional imaging (MRI, CT, ^{11}C-choline PET/CT)

• Age > 18 years Subjects who had signed the ICF at the NM Unit before any study procedure was carried out

Main Exclusion Criteria:

• Subjects who have had radical prostatectomy and/or radiotherapy less than three months prior

• Age <18 years

• Subjects who were unable to provide valid informed consent

Objectives

Primary:

• To evaluate the sensitivity of fluciclovine (^{18}F) (anti-3-18F-FACBC) PET/ computered tomography (CT) in comparison to ^{11}C-choline in identifying a disease relapse.

Secondary:

• To evaluate the predictive value of PET/CT with fluciclovine (^{18}F) (anti-3-^{18}F-FACBC) in relation to progression of the disease

• To evaluate and compare the specificity and diagnostic accuracy of anti-3-18F-FACBC PET/CT using the results obtained from biochemical, clinical and diagnostic tests carried out at baseline evaluation and at follow-up.

Outcomes / endpoints

The primary endpoint was to evaluate the sensitivity of fluciclovine (^{18}F) (anti-3-^{18}F-FACBC) PET/ computered tomography (CT) in comparison to ^{11}C-choline in identifying a disease relapse.

The secondary endpoint was:

- to evaluate the predictive value of PET/CT with fluciclovine (^{18}F) (anti-3-^{18}F-FACBC) in relation to progression of the disease

- to evaluate and compare the specificity and diagnostic accuracy of anti-3-^{18}F-FACBC PET/CT using the results obtained from biochemical, clinical and diagnostic tests carried out at baseline evaluation and at follow-up

Randomisation

This study was non-randomised.

Blinding (masking)

This study was an open-labelled study.

Results

Numbers analysed

97 fluciclovine (^{18}F) PET-CT scans from N=88 patients with recurrent prostate cancer.

Outcomes and estimation

Comparison of Fluciclovine (^{18}F) PET imaging with the results of ^{11}C-Choline PET imaging at Subject level are summarised in the following Table:

Table 24: Summary of Fluciclovine (^{18}F) PET Imaging vs ^{11}C-Choline PET Imaging –Subject Level

		^{11}C-Choline			
	Results n (%)	**Positive**	**Indeterminate**	**Negative**	**Total (N=96)**
Fluciclovine (^{18}F)	**Positive**	31 (32.29%)	1 (1.04%)	6 (6.25%)	38
	Indeterminate	0	4 (4.17%)	3 (3.13%)	7
	Negative	5 (5.21%)	6 (6.25%)	40 (41.67%)	51
	Total	36	11	49	96

N =88 subjects /96 exposures analysed in the analysis set
n= number of lesions meeting the criterion; % = n/number of lesions in analysis*100
Agreement n (%) 75 (78.13 %)
Disagreement n (%) 21 (21.88 %)
Cohen's Kappa = 0.62 [95% CI; 0.48, 0.76] p-value p = 0.0499

The results of PET imaging with fluciclovine (^{18}F) showed a level of agreement with choline (11C) for malignant lesion uptake of 78.13% (75/96) (Cohen's Kappa 0.62 [95% CI; 0.48, 0.76]; p = 0.0499) at Subject level.

Study 3: Blinded Reader Study BED002

A Study to Conduct a Blinded Image Evaluation of Fluciclovine (^{18}F) PET Images and to Evaluate Reader Training for the Interpretation and Inter-Rater Reproducibility of Reading Fluciclovine (^{18}F) PET Scans

- **Study Objectives**

The second BED sponsored trial, BED-002, had several parallel objectives:

- to test the success of a training program to enable readers with no prior experience of reading fluciclovine (^{18}F) PET images to more proficiently read images collected using this tracer
- conduct of a blinded image evaluation (BIE) of images from the 2 prospective studies in recurrent prostate cancer performed at Emory and Bologna University in order to compare diagnostic performance
    - to primary histopathological standard of truth and
    - to ^{11}C-Choline PET-CT using patient data provided for the companion protocol, BED-001.

- **Sample Size and Study participants**

Emory: N=121 fluciclovine (^{18}F) PET-CT scans from 110 patients with recurrent prostate cancer,
Bologna: N=96 fluciclovine (^{18}F) PET-CT scans from 88 patients with recurrent prostate cancer.

Table 25: Subject Disposition for Study BED-002

	Emory	Bologna	Overall
Number of subjects with at least 1 image read	110	88	198
Number of images in Emory analysis set	133	0	133
Number of images in first read	121	0	121
Number of images in intra-reader agreement read	12	0	12
Number of images in Bologna analysis set	0	106	106
Number of images in first read	0	96	96
Number of images in intra-reader agreement read	0	10	10

- **Primary endpoints**

Diagnostic performance: Positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity and detection rate are calculated where possible for individual readers and the overall interpretation (2/3 readers concordance) using histopathological results from biopsy as a reference standard from the Emory data.

The Kappa statistic between fluciclovine (^{18}F) and ^{11}C-Choline was calculated at a lesion level and also at a regional level for individual readers and the overall interpretation (2/3 readers concordance) compared to site

read results of ^{11}C-Choline scans from the Bologna data. For hypothesis testing a one-sided location test was used to do a confirmatory assessment of the agreement data with the set of hypotheses (H_0: Kappa=0.50 vs. H_1: Kappa$\geqslant$0.50).

A detailed rule for 2-out-of-3 reader concordance was set up prior to the study. The analysis was to be performed at lesion, subject and at region level. Exact Confidence intervals were calculated using the method of Clopper and Pearson as two-sided 95% confidence intervals. Endpoints and analysis methods are considered appropriate.

Analysis methods are considered appropriate when a type I error level of 0.025 is applied.

- **Study conduct**

In order to reduce potential bias as far as possible, image reads were performed without any knowledge of any patient data.

Four readers, experienced in PET-CT, but without prior experience of reading images collected following use of fluciclovine (^{18}F), were selected for participation from which three readers, each from a different centre and selected based on availability to complete reads at the ACR facility in Philadelphia were chosen to participate.

Prior to conducting the blinded read, all readers underwent initial training using a standardized training protocol with example cases from the separate training set of images. Following completion of training with successful reader proficiency assessment, each reader was provided with the images from the Bologna and Emory data cohorts. The images were provided in a randomized sequence which was individualized for each reader such that no reader would read the scans in the same order. These scans were allocated a unique identifier specific to each reader, such that it was not possible to link these reports back to the site image read reports collected in BED-001. The randomization list was released only following database lock for study analysis.

- **Randomisation**

Individual subject images had different randomisation codes for each reader. The randomisation codes dictated the order in which the blinded readers viewed the image Datasets.

- **Blinding**

The independent readers were required to be blinded to medical history and outcome of the patients and their histopathology results, and also to results of on-site reads of the fluciclovine (^{18}F) PET-CT scan images and of other imaging methods.

- **Outcomes**

The comparison of blinded read to on site histopathology results followed the same process as described for BED-001; PPV, NPV sensitivity and specificity were calculated and tested using a one sided binomial test.

The lesion level analysis is summarized in the following Table 26:

Table 26: Lesion Level Analysis BIE vs Histopathology Standard of Truth

	Reader 1	Reader 2	Reader 3	Overall	BED001 On Site Read
N	327	361	371	357	371
PPV [95%CI]	98/156 (62.8%)* [54.7, 70.4]	99/148 (66.9%)* [58.7, 74.4]	75/110 (68.2%)* [58.6, 76.7]	98/139 (70.5%) [62.2, 77.9]	126/208 (60.6%)* [53.6, 67.3]
NPV [95%CI]	126/171 (73.7%)* [66.4, 80.1]	157/213 (73.7%)* [67.3, 79.5]	178/261 (68.2%)* [62.2, 73.8]	163/218 (74.8%) [68.5, 80.4]	131/163 (80.4%)* [73.4, 86.2]
Sensitivity [95%CI]	98/143 (68.5%)* [60.2, 76.0]	99/155 (63.9%)* [55.8, 71.4]	75/158 (47.5%) [39.5, 55.6]	98/153 (64.1%) [55.9, 71.6]	126/158 (79.7%)* [72.6, 85.7]
Specificity [95%CI]	126/184 (68.5%)* [61.2, 75.1]	157/206 (76.2%)* [69.8, 81.9]	178/213 (83.6%)* [77.9, 88.3]	163/204 (79.9%) [73.7, 85.2]	131/213 (61.5%)* [54.6, 68.1]

* $p<0.05$

Differences between readers were noted; however, these did not result in significantly different outcomes among readers. Reader 3 consistently reported fewer positive lesions than readers 1 and 2 and reported a higher proportion of false negative outcomes.

Primary Effectiveness vs Histopathological Standard of Truth (Emory Data)

The primary effectiveness endpoints vs histopathological standard of truth (SOT) were calculated using images taken at Emory University vs histopathological results from Emory University as reference standard of truth. Sensitivity, specificity, PPV and NPV were derived and analysed at Lesion, Region and Subject level for individual readers and the overall interpretation.

At **Lesion level**, PPV and NPV significantly exceeded 50% for all three readers. Sensitivity and specificity significantly exceeded 50% for 2/3 readers (Reader 3's sensitivity score was 47.5%).

For **Region 1** (Prostate and Prostate Bed) PPV and NPV significantly exceed 50% for all three readers. Sensitivity significantly exceeded 50% for all three readers, whilst specificity exceeded 50% in 1/3 readers.

For **Region 2** (Pelvic Lymph Nodes), PPV and sensitivity outcomes significantly exceeded 50% for all three readers. No data are presented for NPV and specificity since the number of subjects with negative standard of truth was insufficient to support these analyses.

For **Region 3** (Other Nodal, Bone or Soft Tissues), PPV significantly exceeded 50% for all three readers. Sensitivity exceeded 50% for all three readers.

In a **combined analysis** of all data from extraprostatic sites of recurrence, PPV and sensitivity significantly exceeded 50% for all three readers. No data are presented for NPV and specificity outcomes since the number of subjects with negative standard of truth was insufficient to support these analyses.

At **Subject level** PPV, NPV and sensitivity significantly exceed 50% for all three readers, whilst specificity exceeded 50% in 1/3 readers. The subject detection rate (number of subjects with a positive PET-CT scan) was 84.3%.

Table 27: Subject Level diagnostic performance of blinded reading of fluciclovine (18F) PET-CT vs Histopathology (Emory)

	Reader 1	Reader 2	Reader 3	Overall
PPV	74/98 (75.5%)	71/94 (75.5%)	62/75 (82.7%)	67/85 (78.8%)
NPV	5/5 (100.0%)	7/10 (70.0%)	15/23 (65.2%)	10/16 (62.5%)
Sens	74/74 (100.0%)	71/74 (95.9%)	62/70 (88.6%)	67/73 (91.8%)
Spec	5/29 (17.2%)	7/30 (23.3%)	15/28 (53.6%)	10/28 (35.7%)

Study 4: Blinded Reader Study BED007

A Study to Conduct an Image Evaluation of ^{11}C Choline PET Images from the Bologna study

Kappa values were <0.5 for all comparisons at lesion, region or subject level, which means that the comparison of blinded image evaluation read fluciclovine (^{18}F) PET-CT scans to the blinded expert read ^{11}C-Choline scans failed to demonstrate concordance at lesion, region or subject level.

Insofar, the comparison of BIE read fluciclovine (^{18}F) PET-CT scans to the blinded expert read choline (^{11}C) scans failed to demonstrate concordance at lesion, region or subject level with Kappa values <0.5 in all cases.

Consensus Meeting

Before the conduct of the blinded reader studies BED002 and BED007 on 23 June to 24 June 2014, a fluciclovine reader consensus meeting was held in Bologna, Italy. Six investigators and an independent PET/CT reader without experience in fluciclovine reading were participating. They were involved to set a consensus plan on image reading and the image scanning procedure.

According to the SmPC an acquisition time of 3 minutes per bed position is recommended. An acquisition time 2 min however led to low quality pictures which were difficult to interpret. According to the literature, reduction in acquisition time from 5 to 2 minutes is associated with a significant reduction in image quality[18].

Impact on diagnostic thinking and on patient management

Impact on diagnostic thinking and/or on patient management has to be demonstrated as outlined in Section 4.2.3 of the CHMP Guideline for Clinical Evaluation of Diagnostic Agents (CPMP/EWP/1119/98/Rev. 1). This is usually done in the framework of a clinical study. In this application for marketing authorisation the demonstration of clinical usefulness currently is only demonstrated by some short paragraphs summing up some papers from the literature. Particularly Schuster et al. observed stage change in his prospective study of patients with biochemically recurrent prostate cancer. Fluciclovine (^{18}F) correctly identified 14 more positive prostate bed recurrences (55 vs 41) and 18 more patients with extraprostatic involvement (22 vs 4). As a result fluciclovine (^{18}F) correctly upstaged recurrence in 18 of 70 patients (25.7%).

[18] Brown C, Dempsey M-F, Gillen G and Elliott AT. Investigation of ^{18}F FDG 3D mode PET image quality and acquisition time. Nuc Med Comm 2010; 31: 254-9.

Impact of PSA value on fluciclovine (^{18}F) PET-CT scan performance

With respect to the impact of PSA value on fluciclovine (^{18}F) PET-CT scan performance, PSA value impacted on diagnostic performance on fluciclovine (^{18}F) PET-CT scan in BED-001 study. Focusing on the 99 patients with histopathological confirmation at Emory University in study BED-001, fluciclovine (^{18}F) PET-CT scan cannot be recommended for recurrence imaging in patients with biochemical recurrence after treatment with curative intent and PSA-level ≤1.05 (ng/mL). When PSA was ≤1.05 (ng/mL) (n=16), patient-based sensitivity and specificity were 75% and 66.7%, respectively. For PSA >1.05 - ≤3.98 (n=31), values were 100% and 37.5%, respectively. Sensitivity and specificity were 100% and 20% (n=25) when PSA was >3.98 - ≤8.90. Sensitivity of 100% was obtained when PSA was >8.90 (n=27).

The impact of PSA value on fluciclovine (^{18}F) PET-CT scan performance, the analysis at subject level is summarised in Table 28.

Table 28: Overall Fluciclovine (18F) PET-CT Scan Performance by PSA Quartile for the Entire Emory Site Recurrent Prostate Cancer Population in BED-001 (Subject Level)

	PSA (ng/mL)			
	≤1.05	**>1.05 - ≤3.98**	**>3.98 - ≤8.90**	**>8.90**
No. subj in analysis	16	31	25	27
True Positive (%)	3 (18.8)	23 (74.2)	20 (80)	23 (85.2)
False Positive (%)	4 (25.0)	5 (16.1)	4 (16.0)	4 (14.8)
True Negative (%)	8 (50.0)	3 (9.7)	1 (4.0)	
False Negative (%)	1 (6.3)	0 (0.0)	0 (0.0)	
PPV	3/7	23/28	20/24	23/27
	(42.9)	(82.1)	(83.3)	(85.2)
[95% CI]	[9.9, 81.6]	[63.1, 93.9]	[62.6, 95.3]	[66.3, 95.8]
p-value	0.5000	0.0005	0.0008	0.0002
NPV	8/9	3/3	1/1	
	(88.9)	(100.0)	(100.0)	
[95% CI]	[51.8, 99.7]	[29.2, 100.0]	[2.5, 100.0]	
p-value	0.0195	0.1250	0.5000	
Sensitivity	3/4	23/23	20/20	23/23
	(75.0)	(100.0)	(100.0)	(100.0)
[95% CI]	[19.4, 99.4]	[85.2, 100.0]	[83.2, 100.0]	[85.2, 100.0]
p-value	0.3125	<0.0001	<0.0001	<0.0001
Specificity	8/12	3/8	1/5	
	(66.7)	(37.5)	(20.0)	
[95% CI]	[34.9, 90.1]	[8.5, 75.5]	[0.5, 71.6]	
p-value	0.1938	0.6367	0.8125	
Detection Rate	7/16	28/31	24/25	27/27

	(43.8)	(90.3)	(96.0)	(100.0)
[95% CI]	[19.8, 70.1]	[74.2, 98.0]	[79.6, 99.9]	[87.2, 100.0]
p-value	0.5982	<0.0001	<0.0001	<0.0001

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical efficacy of fluciclovine (^{18}F) should be demonstrated in accordance with the Guideline on Clinical Evaluation of Diagnostic Agents (Doc. Ref. CPMP/EWP/1119/98/Rev. 1, 23 July 2009). Therefore, adequate technical and diagnostic performance of fluciclovine (^{18}F) in relation to a standard of truth and to an established comparator in the clinical context in which the diagnostic agent is to be used should be concluded. Moreover, as fluciclovine (^{18}F) itself may have immediate therapeutic implications, relevant impact on diagnostic thinking and/or patient management in the appropriate clinical context should have been demonstrated as well.

Approximately 40% of patients after potentially curative therapy for prostate carcinoma will develop recurrent disease accompanied by elevated prostate specific antigen (PSA) levels. Accurately detecting the presence of disease confined to the prostate bed versus that of extraprostatic spread to lymph nodes, soft tissue, bone or visceras has profound treatment implications. Excluding recurrences is also crucial.

The 370 MBq dose for fluciclovine (^{18}F) was generally well tolerated and provided a radiation exposure similar to other PET radiopharmaceuticals approved for oncological indications. Studies in Japan incorporated lower doses but extrapolation to Caucasian populations in the EU and USA is not possible as the BMIs differ substantially.

In the clinical development program of fluciclovine (^{18}F) the company attempted to demonstrate the diagnostic performance of fluciclovine (^{18}F) PET-CT against histopathology report (from biopsy or surgical specimen) as standard of truth and Prostascint as comparator (Emory) and against (^{11}C) choline (Bologna). The use of histology is considered the gold standard, an acceptable standard of truth and is in line with the advice provided in the CHMP Guideline for clinical evaluation of diagnostic Agents (CPMP/EWP/1119/98/Rev.1). However, Prostascint (used in Emory) nor choline (^{11}C) (used in Bologna) could be considered accepted comparators as they are not registered in the EU.

Emory study recruited patients originally with localized disease and T3 patients; however, it is not expected that diagnostic performance of fluciclovine (^{18}F) PET-CT is influenced since patients would have been treated accordingly at the time of primary treatment before fluciclovine (^{18}F) PET-CT.

Exclusion in the Emory study of patients under treatment with radiation/cryotherapy in the past 2 years has been justified as to ensure that all patients scanned truly represented biochemical recurrence, and not a PSA bounce.

In addition, fluciclovine (^{18}F) PET-CT images derived from BED001 were obtained from each institution, and were re-read by independent readers in blind to clinical information (study BED-002). These readers were naïve to the use of fluciclovine (^{18}F) but underwent a training programme prior to conducting image evaluation of study images. The independent read data then also compared to a) histopathology (Emory) and b) ^{11}C-choline PET (Bologna). It is acknowledged that the blinded reader study BED-002 Emory can be

considered as supportive evidence on the image reading and evaluation process in study BED-001 Emory but not the BED-002 Bologna since choline (^{11}C) cannot be considered an acceptable comparator. For this same reason, blinded re-reading of choline (^{11}C) PET scans of the Bologna study by an independent expert reader performed in study BED-007 cannot provide supportive data of efficacy of fluciclovine (^{18}F) PET-CT. Data from the pooled analysis in BED-001 Emory has been subjected to a variety of post-hoc subgroup analyses evaluating the impact of various demographic features on scan performance. Subgroup comparisons included age, race, prior treatment for prostate cancer, Gleason score of the primary tumour, D'Amico risk score of the primary tumour, concomitant therapy (including androgen deprivation therapy) and PSA values at the time of scanning, which were considered acceptable subgroup comparisons.

Efficacy data and additional analyses

Diagnostic performance from the BED001 Emory study

The PPV of fluciclovine (^{18}F) PET-CT, using biopsy as SOT, significantly exceeded 50% at Lesion, Region and Subject level, exceeding 90% at Region 2 (pelvic lymph nodes) (95.8%) and Region 4 (extraprostatic) (93.1%), and was statistically significant in each case. A sensitivity analysis allocating the indeterminate lesions as either positive or negative had no statistically significant bearing on the results. NPV was 80.4% at Lesion level and 92.3% at both Subject level and Region level (Region 1). Sensitivity values were higher than 98% at subject level and Region 1 (prostate/prostate bed), Region 2 and Region 4; it was 80% at lesion level. Specificity was 38.7% at Subject level and 30.8% at Region 1, and 61.5% at Lesion level. NPV and specificity analyses were not conducted at Regions 2 and 4 since the number of subjects with negative standard of truth was insufficient. Therefore, fluciclovine (^{18}F) PET-CT met the success criteria for patient-based sensitivity (higher than 80%), with an excellent result of 98.6% (95%CI: 92.7-100)) while specificity was really disappointing and very far away for the anticipated one (90%) and the success criteria (higher than 80%).

The detection rate (DR) exceeded 80% at Subject and Region level ($p<0.0001$), and was 100% for Regions 2 and 4. The DR at lesion level was 56.1%. Sensitivity analysis had no statistically significant bearing on the data. Detection rate (i.e. positivity rate) is a variable of no clinical interest since it refers only to the number of scans considered as positive versus the total number of scans performed. It is not related to the histological result of the positive findings and therefore not relevant in terms of demonstrating diagnostic performace of the product.

The calculated positive likelihood ratio of fluciclovine (^{18}F) PET-CT to detect recurrences was 1.61 and negative likelihood ratio of 0.035 at the subject level. The larger the positive likelihood ratio, the greater the likelihood of disease while the smaller the negative likelihood ratio, the lesser the likelihood of disease. As a consequence, this test seems to be poor at confirming suspected recurrence of prostate cancer but excellent to exclude suspected recurrence of prostate cancer since a negative result on a fluciclivine scan is almost sure to show a true negative.

Using the findings of other relevant imaging modalities, the PPV of fluciclovine (^{18}F) PET-CT scanning significantly exceeded 50% in Regions 1 – 3 in all but 1 instance. The lowest agreement was approximately 64% in Region 1 and the highest was 100% in Regions 2 and 3, for fluciclovine (^{18}F) PET-CT vs MRI in each instance. Agreement between fluciclovine (^{18}F) PET-CT and unenhanced CT scanning was 18% in Region 1, due to the poor detection of prostate lesions by unenhanced CT.

Fluciclovine (^{18}F) PET-CT scanning detected more sites of prostate cancer recurrence than the other imaging modalities. This superior performance was most apparent in Region 1 (Prostate and Prostate bed) where

fluciclovine (^{18}F) PET-CT scanning identified 9 more positive lesions than unenhanced CT scanning and 3 and 4 more than enhanced CT scanning and MRI, respectively.

Sub-group analyses revealed that there was no obvious impact of age, race, prior cancer treatment, and Gleason score or D'Amico risk score of the primary tumour on fluciclovine (^{18}F) PET-CT scan performance.

Concerning the impact of PSA value on fluciclovine (^{18}F) PET-CT scan performance, there was generally a lower sensitivity in subjects in the first quartile of PSA values (PSA≤1.05 ng/mL) compared to PSA levels above 1.05 ng/mL. This was related to the number of true positives which was much lower (18.8%) in patients with PSA values <1.05 ng/mL compared to PSA values >1.05 - ≤ 3.98 ng/mL (74.2%) and patients with PSA value above 3.98 ng/mL (80-85.2%). Specificity was generally low for any PSA value but more so in patients with PSA values above 1.05 ng/mL. Therefore, there is a warning stated in section 4.4 of the SmPC that the PSA value may affect the diagnostic performance of fluciclovine (^{18}F) PET. (see section 5.1, Pharmacodynamic properties).

False-positive and false-negative results of fluciclovine (^{18}F) PET-CT were discussed. The majority of false positive and false negative scans reported were from findings in the prostate/prostate bed. There were 19 false positive cases, and the majority of the patients had been previously treated with radiotherapy. Review of these cases indicated that the histopathology report showed 'radiation artefact'. There was 1 patient with fibrous tissue and 1 patient with inflammatory response in a cryotherapied tissue there were no false positives or false negatives from local regional nodal lesions biopsied.Therefore, the SmPC contains a statement in section 4.4 that false-positive cases have been also attributed to fibrous tissue, inflammatory response in a cryotherapied tissue and radiation artefacts in patients previously treated with radiotherapy.

Diagnostic performance from the BED002 study

In supportive study BED-002 with central blinded reading of fluciclovine (^{18}F) PET-CT images, patient-based sensitivity values to detect suspected prostate cancer recurrence versus histopathology were high (i.e. 91.8% (67/73) overall and higher than 88% for all three readers), just a little lower than sensitivity obtained using the onsite read findings (98.6%). And specificity values were disappointing, both overall (35.7%) and for each reader (17.2-53.6%), as it happened for the onsite read. In the total of 58 lesions in the prostatic region and histological proof, overall sensitivity and specificity was 91.4% and 48.7%, respectively (with the onsite read respective values were of 98.3% and 30.8%). In the extra-prostatic region in which 26 lesions had histopthological proof of involvement, overall sensitivity was 88.5% for the blinded re-reads (and 100% for the onsite reads) with specificity not evaluable.

Impact on diagnostic thinking and/or on patient management

Generally, a well-designed post-authorization prospective study is required to assess the impact of fluciclovine (^{18}F) on the diagnostic thinking and patient management in the intended clinical context and intended population and ideally versus the impact of an established comparator. There are however, two ongoing company-sponsored studies BED-003 and BED-004 to assess the impact on the patient management of fluciclovine (^{18}F) in patients with suspicion of recurrent prostate carcinoma after presumed definitive therapy for primary disease based on raised PSA values. The full protocol of these studies was provided. None is addressing the impact on the diagnostic thinking, which will remain unknown, but study BED-004 will also analyze the impact on clinical outcome. Both studies are crucial to know the clinical efficacy of this radiopharmaceutical in the clinical context in which is intended to be used. The CHMP recommends the applicant to provide study results from both trials as soon as they are available.

Interpretation of fluciclovine (18F) images and limitations of use

Fluciclovine (^{18}F) images should be interpreted visually by appropriately trained personnel. Quantitative/semiquantitative measurement of fluciclovine (^{18}F) uptake should not be used for clinical interpretation of these images as the impact of quantitative/semiquantitative measurement of fluciclovine (^{18}F) uptake as an aid to image interpretation has not been assessed.

PET images with fluciclovine (^{18}F) should be interpreted visually. Suspicion of cancer in sites typical for prostate cancer recurrence is based on fluciclovine (^{18}F) uptake in comparison with tissue background. For small lesions (<1 cm diameter) focal uptake greater than blood pool should be considered suspicious for cancer. For larger lesions, uptake equal to or greater than bone marrow is considered suspicious for cancer.

Image interpretation errors can occur with PET with fluciclovine (^{18}F) (see section 5.1).

Fluciclovine (^{18}F) uptake is not specific for prostate cancer and may occur with other types of cancer, prostatitis and benign prostatic hyperplasia. False-positive cases have been also described in association with an inflammatory response after cryotherapy and radiation artefacts in patients previously treated with radiotherapy. Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, should be considered where appropriate.

The use of either intravenous iodinated CT contrast or oral contrast media is not required to interpret fluciclovine (^{18}F) PET images.

Diagnostic performance of fluciclovine (^{18}F) to detect recurrences has not been investigated in patients with a suspected recurrence based on elevated blood PSA levels after primary radical treatment and with a recent positive whole-body bone scintigraphy.

The detection of prostate cancer recurrence in prostate/prostate bed, regional lymph nodes, bone, soft tissue and non-regional lymph nodes by fluciclovine (^{18}F) PET has been reported. However, no evidence has been provided of prostate cancer recurrence in other regions of the body.

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should, in every case, be as low as reasonably achievable to obtain the required diagnostic information.

For information on use in the paediatric population, see section 4.2 of the SmPC.

2.5.4. Conclusions on the clinical efficacy

The BED001 Emory study showed that fluciclovine (18F) PET-CT has an excellent overall sensitivity of 98.6% but a low specificity of 38.7% (considering combined local, regional lymph nodes and distant sites) in relation to a standard of truth (histology report from biopsy or surgical specimen) to detect prostate cancer recurrences in patients with a suspected recurrence based on elevated blood PSA levels after curative treatment of the localised primary tumour. All patients had a recent negative whole-body bone scintigraphy. No data on patients with distant recurrence in other regions of the body apart from non-regional lymph nodes, bone or soft tissue was provided. Fluciclovine (^{18}F) images should be interpreted visually.

Additional results of the reader study BED002 supported the primary findings as the scans were compared with histopathology, an acceptable standard of truth. False-positive cases have been described in prostate or prostate bed.

Therefore, taking into account the data from the BED001 Emory study as well as the blinded reading in

BED002, the technical and diagnostic performance of fluciclovine to detect the sites of recurrence in prostate cancer patients that have suspected recurrence based on PSA levels after primary curative treatment can be considered demonstrated.

The CHMP recommends the following measures to assess the impact of fluciclovine (^{18}F) on diagnostic thinking and patient management:

- Impact on diagnostic thinking and/or on patient management in the intended clinical context and intended population to be further evaluated in currently running studies, BED-003 and BED-004.

2.6. Clinical safety

Safety data relevant for characterisation of the fluciclovine's safety profile is derived from seven completed sponsored studies, six of which were prospective studies and additional patients from the company's open access program. Safety is evaluated for the retrospective observational study (**BED001**) which collected safety data from all patients available at the four centres in the US (1 site) and EU (Italy (1 site) and Norway (2 sites).

The following table provides an overview about these clinical studies and the subjects included:

Table 29: Summary of clinical studies with fluciclovine (18F) solution for injection

Study No./ Sponsor	Study Design	Population	No. Subj Enrolled/ Evaluablefor Safety	Study & Control drugs	Objectives/endpoints
Phase I					
GE148-001 GE Healthcare	Open label, single dose	Healthy volunteers Primary prostate cancer	6/6 [3M/3F] 6/6	Fluciclovine (^{18}F)	Safety, biodistribution, kinetics and dosimetry in HVs Safety, uptake and retention in biopsy-proven prostate cancer
NMK36-P1 NMP	Open label, single dose	Healthy volunteers	6/6	Fluciclovine (^{18}F)	Safety, kinetics, biodistribution and dosimetry
Phase II prospective studies in prostate cancer					
GE148-002 GE Healthcare	Open label, single dose	Primary prostate cancer	25/22	Fluciclovine (^{18}F)	Safety and proof of concept efficacy data
NMK36-PC-201 NMP	Open label, single dose	Primary prostate cancer	11/10	Fluciclovine (^{18}F)	Safety, dose ranging and proof of concept efficacy data
NMK36-PC-202 NMP	Open label, two dose, single administration	Primary prostate cancer patients and patients with advanced primary disease and known metastases	72/68	Fluciclovine (^{18}F)	Efficacy and safety in untreated prostate cancer subjects destined for prostatectomy or hormone therapy.
Phase II prospective studies in glioma					
NMK36-BT-201 NMP	Open label, single dose	Glioma	5/5	Fluciclovine (^{18}F)	Safety, dose ranging and proof of concept efficacy data
Phase III retrospective observational study in prostate and other cancers					

BED001	Retrospective, observational	Recurrent & primary prostate cancer Breast cancer	714/714	Fluciclovine (^{18}F)	Retrospective observational safety and effectiveness study of patients exposed to fluciclovine (18F)

As most of the trials in this application are small and included also in the **BED001** population, main safety information can be derived from this analysis.

Patient exposure

Safety data in this application includes information from a total of 837 subjects as follows:

- 12 healthy volunteers (studies GE148-001 (n=6) and NMK36-P1 (n=6))
- 596 males diagnosed with recurrent prostate cancer (study BED001 (n=596))
- 201 males diagnosed with primary prostate cancer (studies GE148-001 (n=6), GE148-002 (n=22), NMK36-PC-201 (n=10); NMK36-PC-202 (n= 68); and BED001 (n=95)
- 28 subjects diagnosed with other types of cancer (NMK36-BT-201: glioma (n = 5); study BED001: breast cancer (n=9), parathyroid adenoma (n=3), glioma (n=9) and other (n=2)).

The mean (± SD) dose of fluciclovine (^{18}F) in the BED001 study across the 4 sites was 309.18 (± 60.640) MBq and the median dose was 305.65 MBq.

In all the GE and NMP sponsored studies, fluciclovine (^{18}F) was given as a single administration. In the BED001 study, experience from repeat use of the radiopharmaceutical was noted. Subjects here received up to 5 administrations of fluciclovine (^{18}F).

Adverse events

Events which may be considered to be related to administration of fluciclovine (^{18}F) include: transient dysgeusia, injection site reactions (pain, redness at injection site), parosmia. The following table describes the ADRs observed with fluciclovine. Adverse reactions were reported commonly (≥ 1/100 to < 1/10) during clinical trials. They are listed below by MedDRA body system organ class.

Table 30: Adverse Reactions to Fluciclovine

System Organ Class/Preferred Term	Frequency	Intensity		
	Number of Subjects (%) Total N =	Mild	Moderate	Severe
Any event	**12 (1%)**	**12**	**0**	**0**
General disorders and administration site	**7 (0.6%)**	**7**	**0**	**0**
Injection-site reactions	7 (0.6%)	7	0	0
Nervous system disorders	**4 (0.3%)**	**3**	**0**	**0**
Dysgeusia	4 (0.4%)	3	0	0
Respiratory Organ, Thoracic and Mediastinal Disorders	**2 (0.2%)**	**2**	**0**	**0**
Parosmia	2 (0.2%)	2	0	0

Injection side pain may be induced by the higher osmolality of the product of about 520 mOsm/Kg. Most important, there were no reports of hypersensitivity reactions from the exposed patients.

Serious adverse event/deaths/other significant events

No serious adverse events were reported in the GE or NMP-sponsored studies.

In the retrospective trial BED-001, two patients experienced a serious adverse event within the month following exposure to fluciclovine (^{18}F).

None of these events was considered to be related to fluciclovine (^{18}F).

No deaths were reported in any study or for any patient exposure, including within 35 days of administration of fluciclovine (^{18}F) in the BED001 study.

Laboratory findings

Table 31: Change from Baseline Haematology Values

	Haemo-globin [g/dL] N=134	HCT [%] N=105	RBC 10^{12}/L N=102	MCV [fL] N=101	MCH [pg] N=101	MCHC [g/dL] N=100	WBC [10^9/L] N=125	ANC [10^9/L] N-42	PLT [10^9/L] N=124
Mean	-0.40	-1.39	-0.165	-0.04	0.02	0.05	0.16	-0.05	-5.1
SD	1.23	3.37	0.46	1.04	0.62	0.62	2.433	1.38	26.03
Median	-0.10	-0.50	-0.09	0	0	0.05	-0.10	0.02	-5.0
Min;Max	-5.5; +1.6	-17.0; +6.1	-2.36; +0.63	-2.6; +3.1	-3.0; +1.4	-2.0; +1.6	-11.5; +11.4	-5.80; +2.60	-85; +112

Table 32: Change from Baseline Biochemistry Values

	Urea [mmol/L] N=98	Creati-nine [umol/L] N=129	ALT [U/L] N=102	AST [U/L] N=94	ALP [U/L] N=106	BILI [umol/L] N=25	Na [mmol/L] N=111	K [mmol/L] N=112
Mean	0.06	1.21	-1.8	-0.6	0.7	-0.38	-0.3	-0.01
SD	1.42	16.74	5.51	6.2	18.59	4.99	2.41	0.44
Median	-0.00	0.88	-1.5	0.0	-1.0	0.00	0.0	0.0
Min;Max	-4.61; +4.99	-40.6; +129	-25; +20	-23; +22	-24; +174	-17; +8.55	-7; +5	-0.8; +1.7

	Cl [mmol/L] N=95	Ca [mmol/L] N=108	Random glucose [mmol/L] N=51	CO_2 H [mmol/L] N=88	Cr Cl [ml/min] N=58	GFR [mL/min] N=86
Mean	0.5	-0.05	0.36	-0.3	1.02	0.64
SD	2.78	0.15	1.71	2.75	15.31	10.71
Median	1.0	0.03	0.33	-0.5	1.75	0.90
Min;Max	-7; +7	-1.03; +0.20	-4.37; +5.86	-7; +10	-72.2; +45.8	-31.95; 30.54

Table 33: Urinalysis

	Specific Gravity N=75	pH N=75
Mean	0.00	0.06
SD	0.00	1.01
Median	0.00	0.00

Min;Max	-0.02; +0.02	-2.5; +2.5

No clinically significant abnormalities of vital signs or ECGs attributable to fluciclovine (^{18}F) administration were observed in the GE and NMP sponsored trials.

Safety in special populations

The number of exposures of fluciclovine (^{18}F) in the elderly population and their profile of related adverse reactions in the safety database was provided.

Since the first dose in humans to 27th November 2016, an estimated 2638 subjects have received at least one dose of fluciclovine. Exposure has accumulated from completed/ongoing sponsored studies (N=1153), special use license in Norway (N=1141), post marketing commercial use in the USA (N=118) and ongoing investigator sponsored studies (N=226).

In the elderly population, the company initially provided with the safety information from the exposure of fluciclovine (^{18}F) only from the company-sponsored trial BED-001 (n=405). A total of 12 in BED-001, independently of age, were described:

- 9 extravasation (potentially due to poor injection technique under the company's view)
- 1 case of malaise, pain, constipation (all in 1 patient), decreased haemoglobin (1 patient) and increased creatinine (1 patient) that the company consider not related to fluciclovine (^{18}F) but to other contrast agents or concomitant diseases. These are considered not related to flucicovine (^{18}F) but to the concomitant use of diagnostic agents or concomitant diseases by the company

The overall exposure up to January 2017 in the two currently ongoing company-sponsored trials BED-003 and BED-004 and nine trials sponsored by other companies have been now reported. This increase the overall safety database in 438 patients from which 224 were patients aged at least 65 years. The related adverse events in the overall population included were 12:

- 7 subjects with injection site reactions, 6 of which occurred in patients aged >65 years.
- 5 subjects with dysgeusia and/or parosmia.

The applicant does not know how many doses of fluciclovine (^{18}F) have been administered spefically in elderly in the special use licensed in Norway (N=1141), postmarketing commercial use in the USA (N=118) and ongoing investigator sponsored studies (N=226). However, only 1 adverse event was reported and considered by the investigator as unrelated to receipt of fluciclovine.

Therefore, the applicant has updated the safety table including only 12 cases (1%) from the ongoing/completed sponsored studies (N=1153), related adverse events are 7 injection-site reactions, and 3 cases of dysgeusia and 2 parosmia.

Safety related to drug-drug interactions and other interactions

The applicant stated that no human studies of potential drug interactions have been conducted to date. Furthermore, no suggestion of drug interactions has been detected in the clinical data submitted in this application. Fluciclovine (^{18}F) is not subject to metabolism and is not a substrate for renal drug transporters and therefore drug interactions would not be expected.

Furthermore, nor safety issues are raised from assessment with respect to the other categories listed in this section (potential drug abuse, withdrawal and rebound, as well as with respect to effects on ability to drive or operate machinery or impairment of mental ability).

Discontinuation due to adverse events

There were no adverse events which led to study discontinuation in any of the studies.

Post marketing experience

See section on specialpopulations.

2.6.1. Discussion on clinical safety

Overall, the sample exposed to a single administration of fluciclovine (^{18}F) in the safety database is 596 males diagnosed with recurrent prostate cancer (study BED001 (n=596) and 201 males diagnosed with primary prostate cancer [studies GE148-001 (n=6), GE148-002 (n=22), NMK36-PC-201 (n=10); NMK36-PC-202 (n= 68); and BED001 (n=95)].

The mean (± SD) dose of fluciclovine (^{18}F) in the BED001 study across the 4 sites was 309.18 (± 60.640) MBq whereas the recommended activity for an adult is 370MBq fluciclovine. This activity is well in the range of a diagnostic radiopharmaceutical and no dose-effects are expected.

Fluciclovine (^{18}F) was generally well tolerated. ADRs of fluciclovine (^{18}F) include: transient dysgeusia, injection site reactions (pain, redness at injection site), nausea, malaise, constipation and headache. Overall, these events are rare, occurring in ≤ 0.2% of patients exposed to fluciclovine (^{18}F). Most important, there were no reports of hypersensitivity reactions from the exposed patients.

No deaths and only two serious adverse events have been reported; none of the SAEs was considered related to the study drug, the administration, or the imaging procedure.

There were small changes in lab parameters and vital signs, but most appeared non-detrimental and of no clinical relevance.

The human radiation dosimetry of Fluciclovine (^{18}F) yields an effective dose of 22 µSv/MBq. The results of weight-adjusted calculations show no significant differences over the range of 50 to 80 kg body mass. Therefore no dose adjustments on patient's weight were done.

Specifications related to radiation protection in the context of manipulation and elimination of the radiopharmaceutical by healthcare professionals, and radiation protection for the family, as appearing in the SmPC in section 6.6 were considered appropriate and in accordance with those approved for other fluorine (^{18}F) radiopharmaceuticals.

Safety information for repeated injections is limited (up to 5); however, no worsening of adverse event of other signal for increase of toxicity was reported.

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

Axumin has not been studied in patients with renal or hepatic impairment and no specific safety data in patients with impaired renal function or impaired hepatic function have been provided. In these cases, the higher irradiation in the body caused by slower hepatic and/or renal clearance of the radiopharmaceutical itself or their radioactive metabolites should be taken into account. Careful consideration of the benefit/risk ratio in these patients is required since an increased radiation exposure is possible.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 8.2 mSv when the maximal recommended activity of 370 MBq is administered these adverse reactions are expected to occur with a low probability. The important potential risk of contact with radiation (carcinogenic and hereditary risk) has beenincluded in the RMP.

Fluciclovine (^{18}F) has no or negligible influence on the ability to drive and use machines.

In the event of administration of a radiation overdose with fluciclovine (^{18}F) the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis, frequent micturition and defecation. It might be helpful to estimate the effective dose that was applied.

Fluciclovine is contraindicated in patients with hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 of the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The patient should be encouraged to drink sufficient amounts and void as often as possible during the first hours after the scan in order to reduce radiation exposure of the bladder.

Close contact with infants and pregnant women should be restricted during the initial 12 hours following the injection.

This medicinal product contains up to 39 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

General warning

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

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

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

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

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

2.6.2. Conclusions on the clinical safety

No serious adverse reactions have been observed during the conduct of the clinical studies. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose of fluciclovine (^{18}F) is 8.2 mSv, there is a low probability for any effects resulting from ionising radiation when the maximal recommended activity of 370 MBq is administered. The safety has been adequately characterised and considered acceptable.

2.7. Risk Management Plan

Safety concerns

Table 34: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Injection site reactions
Important potential risks	• PET imaging interpretation errors • Off-label use • Risk due to contact with radiation (carcinogenic and hereditary risk)
Missing information	• Patients with impaired renal function • Patients with impaired hepatic function

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 35: Summary table of risk minimisation measures by safety concerns

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Injection site reactions	Ensure awareness.	None

	Appropriate statements and warnings are included in the product information. SmPC 4.2. Posology SmPC 4.8. Undesirable effects PIL 3. What you need to know before you use Axumin PIL 4. Possible side effects	

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important potential risks		
PET Imaging interpretation errors	Appropriate statements and warnings are included in the product information. SmPC 4.4 Special Warnings and Precautions for Use PIL 3. How Axumin will be used	Provision of reader training program (self training program and self assessment test images) in association with European Association of Nuclear Medicines (EANM) and national societies
Off-label use	Provide clear prescribing information. Appropriate statements and warnings are included in the product information. SmPC 4.2. Posology and Method of Administration SmPC 4.4 Special Warnings and Precautions for Use PIL 3. How Axumin will be used	None.
Risk due to contact with radiation (carcinogenic and hereditary risk)	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.4 Special Warnings and Precautions for Use SmPC 4.6. Fertility, Pregnancy and Lactation PIL 1. What Axumin is and what it is used for PIL 3. How you will be given Axumin	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important missing information		
Patients with impaired renal function	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.4 Special Warnings and Precautions for Use PIL 2. What you need to know before you use Axumin	None
Patients with impaired liver function	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.4 Special warnings and Precautions for Use PIL 2. What you need to know before you use Axumin	None

2.8. Pharmacovigilance

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.

2.9. New Active Substance

The applicant compared the structure of fluciclovine with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Axumin (fluciclovine (^{18}F)) 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

Prostate cancer is the most common cancer in elderly males (> 70 years of age) in Europe. It is a major health concern, especially in developed countries with their greater proportion of elderly men in the general population. Primary curative procedures such as radical prostatectomy and radiotherapy are well-established therapeutic options in the management of localised prostate cancer. Despite technical improvements, there is still a significant risk of cancer recurrence after therapy. Between 27% and 53% of all patients undergoing radical prostatectomy or radiotherapy develop PSA-recurrence. A rising PSA level universally precedes metastatic progression. Measurement of PSA is a cornerstone in follow-up after local treatment. However, local recurrence after curative treatment is possible without a concomitant rise in PSA level and has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. Once a PSA relapse has been diagnosed, it is important to determine whether the recurrence has developed at local or distant sites. Determining the location of the recurrence is critical, as this defines optimal choice of therapy.

3.1.2. Available therapies and unmet medical need

The diagnostic accuracy of standard imaging tests (ultrasound, CT and MRI) for the identification of sites of prostate cancer recurrence is low. Almost 90% of the standard battery of imaging tests, may be negative.

Nuclear imaging techniques have been utilised for the detection of recurrent prostate cancer for a number of years. Bone metastases, one of the most frequent location of metastases from prostate cancer, are generally detected using technetium (^{99m}Tc) ddiphosphonates with not infrequent false-positive cases and by sodium

fluoride (^{18}F). The most widely used PET radiopharmaceutical, the glucose analogue fludeoxyglucose (^{18}F), is not generally used as an imaging agent in prostate cancer due to indolent growth of many prostate cancers and the high urinary excretion of fludeoxyglucose (^{18}F) making reliable, good quality imaging difficult in this patient population. Alternative radiopharmaceuticals with different mechanisms of action and a comparable diagnostic performance to overcome these limitations are needed.

Currently, PET imaging with choline radiopharmaceuticals have been used in the diagnostic work-up of prostate cancer recurrences. However, choline (^{11}C) is neither registered in the EU nor has it been validated as a diagnostic agent for prostate recurrences. Moreover, the 20 minute half-life of ^{11}C limits the use of this agent to medical centres with on-site ^{11}C production capability, which prevents this agent from being supplied via the established PET supply chain. Substitution of Fluorine-18 (^{18}F) for ^{11}C enables offsite production and commercial supply due to the longer (110 minute) half life of ^{18}F. Fluorocholines (^{18}F) are registered in some EU countries with specific indications for the detection of recurrences depending on the particular commercial product.

Fluciclovine (^{18}F) is a PET tracer that visualizes the increased amino acid transport associated with tumour cells in comparison to normal tissues because it is a substrate for amino acid transporters upregulated in prostate cancer cells. It also claims a lack of incorporation into protein which avoids potential safety implications of introducing synthetic amino acids into proteins.

3.1.3. Main clinical studies

3.2. Favourable effects

Evidence for efficacy of fluciclovine(^{18}F) PET is mainly based on the R01/BED001 Emory study as pivotal and the BED002 blinded reader results on patients from the Emory site as supportive.

In the BED001 Emory population the PPV of fluciclovine (^{18}F) PET-CT, using biopsy as SOT, significantly exceeded 50% at Lesion, Region and Subject level, exceeding 90% at Region 2 (pelvic lymph nodes) (95.8%) and Region 4 (extra-prostatic) (93.1%), and was statistically significant in each case. A sensitivity analysis allocating the indeterminate lesions as either positive or negative had no statistically significant bearing on the results. Patient-based sensitivity of fluciclovine (^{18}F) PET-CT scans versus histopathology for detection of recurrent prostate cancer (combining both local, regional lymph nodes and distant disease) was 98.6% (95%CI: 92.7-100%); this value met the anticipated sensitivity (90%) and the success criteria (higher than 80%). Negative likelihood ratio was good (0.035). Therefore, an excellent sensitivity and negative likelihood ratio makes fluciclovine (^{18}F) PET-CT a good test to exclude suspected recurrences.

In the Emory population of the blinded inter-reader comparison study BED002, with histopathology as standard of truths, patient-based sensitivity values to detect suspected prostate cancer recurrence versus the standard of truth were high (i.e. 91.8% (67/73) overall and higher than 88% for all three readers), just a little lower than sensitivity obtained using the onsite read findings (98.6%) detailed hereinabove. Inter-reader agreement amongst the three readers when reading the Emory images was 94.7%, 74.4% and 70.3% at Lesion level and Region level for Regions 1 and 4, with associated Kappa greater than or equal to 0.5.

3.3. Uncertainties and limitations about favourable effects

In BED001 Emory patient-based specificity for detection of (local, regional lymph nodes and distant) recurrent prostate cancer versus the standard of truth were as low as 38.7% (95% CI: 21.8-57.8%). The positive likelihood ratio was 1.61. The product seems to be of limited value for the confirmation of suspected recurrence of prostate cancer, with a relatively high number of false positive cases versus histopathology (19/99) reflecting the limitations of the test for confirmation of recurrences. The false positives reported were from findings in the prostate/prostate bed. Among the false positive cases, one had fibrous tissue, other case with inflammatory response to cryotherapy and the remaining cases had been previously treated with radiotherapy showing a 'radiation artefact' in the histopathology report. Therefore, the indication has included a statement on the limitation in the interpretation of a positive scan. The errors in interpretation of the scans have been included in the RMP as an important potential risk and a special warning has been included in section 4.4 along with a description of the high sensitivity and low specificity in section 5.1 of the SmPC. In addition, the applicant has been requested to implement additional risk minimization measures to ensure that in each Member State where Axumin is marketed, all Healthcare professionals who are expected to use Axumin have access to self-training educational material in order to reduce the risk of PET imaging interpretation errors. The key elements are described in Annex IID and in the RMP.

In study BED-002 with central blinded reading of fluciclovine (^{18}F) PET-CT images from BED-001 study at Emory University, specificity values were also disappointing, both overall (35.7%) and for each reader (17.2-53.6%). Inter-reader agreement amongst the three readers was 76.0% at the Subject level with Kappa 0.36. As Reader 1 and Reader 2 had generally higher inter-reader agreement with each other than with Reader 3, the results may have been biased by a low number of readers and worsened by results from the third reader.

Diagnostic performance of fluciclovine (^{18}F) to detect recurrences has not been investigated in patients with a suspected PSA-based recurrence after primary radical treatment and with a recent positive whole-body bone scintigraphy. Therefore, information has been included in section 4.4 and 5.1 to inform the prescriber that patients in the study with suspected resurrence of prostate cancer had a negative bone scintigraphy before undergoing fluciclovine (^{18}F) PET-CT.

The PSA value affected the diagnostic performance of fluciclovine (^{18}F) PET to detect prostate cancer recurrences (see section 5.1, Pharmacodynamic effects).

The CHMP has recommended that impact on diagnostic thinking and/or on patient management in the intended clinical context and intended population would be further evaluated in currently running studies (BED-003 and BED-004) and that the data should be submitted for assessment.

The BED 001 Emory data were generated in a prospective study with conclusions based mainly on retrospective analyses. The retrospective nature of the analyses is a source of potential for selection bias, which can be considered as the main uncertainty in the results of the blinded readings. However, procedures according to GCP standards implemented for retrospective data collection from patient records are appropriate to ensure data quality.

3.4. Unfavourable effects

The adverse reactions for fluciclovine (^{18}F) administration include dysgeusia, injection site reactions (pain, redness at injection site) and parosmia.

Overall, these events are rare and mild, occurring in ≤0.2% of patients exposed to fluciclovine (^{18}F). This is in line with the experience from other F-18 based radiopharmaceuticals for which no serious adverse reactions have been observed to date.

There is the potential for misinterpretation of the PET images acquired following administration of Axumin. Such interpretation errors may result in inappropriate treatment. Therefore, this issue is assessed as an important potential risk in the RMP.

Moreover, there is the potential for the product to be used for other diagnostic situations beyond the precise indication applied for which is also considered to be an important potential risk in the RMP.

As the effective dose of fluciclovine (^{18}F) is 8.2 mSv when the maximal recommended activity of 370 MBq is administered, adverse reactions due to radiation are expected to occur with a very low probability.

3.5. Uncertainties and limitations about unfavourable effects

The safety information in patients that have received repeated injections is limited (up to 5); however, no worsening of adverse reactions or new adverse reactions is expected.

There were small changes in lab parameters and vital signs that have been observed. However, these are considered of no clinical relevance.

Fluciclovine (^{18}F) is expected to be used in special populations such as elderly and patients with renal or hepatic impairment. The applicant has provided safety information of fluciclovine (^{18}F) in the elderly population. However, there are no specific safety data in patients with impaired renal function or impaired hepatic function that have been provided. This has been included as missing information in the RMP.

3.6. Effects Table

Table 36: Fluciclovine (18F) for positron emission tomography (PET) imaging of adult men with suspected prostate cancer recurrence

Effect	Short Description	On site read	Blinded read	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Sensitivity	**Lesion-based**	79.7%	64.1%			Based on Emory R01 BED001 and BED 002 data see part on clinical efficacy
Sensitivity	**Prostatic**	98.3%	91.4%			
Sensitivity	**Extra-prostatic**	100.0%	88.5%			
Sensitivity	**Patient-based**	98.6%	91.8%			
Specificity	**Lesion-based**	61.5%	79.9%			
Specificity	**Prostatic**	30.8%	48.7%			

Effect	Short Description	On site read	Blinded read	Control	Uncertainties / Strength of evidence	References
Specificity	**Extra-prostatic**	0.0%	0.0%			
Specificity	**Patient-based**	38.7%	35.7%			
PPV	**Lesion-based**	60.6%	70.5%			
PPV	**Prostatic**	67.9%	72.6%			
PPV	**Extra-prostatic**	93.1%	92.0%			
PPV	**Patient-based**	79.3%	78.8%			
NPV	**Lesion-based**	80.4%	74.8%			
NPV	**Prostatic**	92.3%	79.2%			
NPV	**Extra-prostatic**	0.0%	0.0%			
NPV	**Patient-based**	92.3%	62.5%			
Unfavourable Effects						
Injection site reaction	%	0.6%				
Dysgeusia	%	0.4%				
Parosmia	%	0.2%				

Abbreviations: PPV Positive predictive value, NPV negative predictive value Notes: none

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The applicant has presented data showing the efficacy of fluciclovine (18F) to exclude recurrences in patients that had undergone primary curative treatment of localised primary prostate cancer and have suspected recurrence of prostate cancer and a recent negative whole-body bone scintigraphy, giving its excellent sensitivity and negative likelihood ratio. For the treating physician, exclusion of recurrences is an important aspect for the diagnostic work-up and patient management of biochemically suspected recurrent prostate cancer. Since fluciclovine has very low specificity and positive likelihood ratio, it is not intended to be used to confirm recurrences. Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, should be considered for positive scans to confirm recurrence of prostate cancer.

The applicant has presented data showing the efficacy of fluciclovine (^{18}F) to exclude recurrences in patients that had undergone primary curative treatment of localised primary prostate cancer and have suspected recurrence of prostate cancer and a recent negative whole-body bone scintigraphy. Fluciclovine (^{18}F) is not intended to confirm recurrences, hence providing giving its excellent sensitivity and negative likelihood ratio and very low specificity and positive likelihood ratio. For the treating physician, exclusion of recurrences is an important aspect for the diagnostic work-up and patient management of biochemically suspected recurrent prostate cancer.

It has been recommended to submit the results of study BED-003 and BED-004 to assess the impact of fluciclovine (^{18}F) on the diagnostic thinking and on patient management ideally versus the impact of an established comparator.

Some uncertainty remains whether presumably false positive readings of fluciclovine (^{18}F) -PET images may either result in wrongly diagnosed recurrent prostate cancer or the fluciclovine (^{18}F) PET-CT may be picked up by benign lesions such as BHP. Therefore, risk minimisation measures have been implemented to inform the readers on the interpretations of the scans.

Axumin was well tolerated and no serious safety risks have been described with this radiopharmaceutical. For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should, in every case, be as low as reasonably achievable to obtain the required diagnostic information.

3.7.2. Balance of benefits and risks

Early diagnosis of recurrence of prostate cancer and exclusion of recurrences can have an impact on the further course of the disease and the treatment algorythm. The detection or exclusion of extra-prostatic spread/metastases by fluciclovine (^{18}F) PET-CT can have a significant impact on the choice of treatment.

Fluciclovine (^{18}F) PET-CT is expected to have an advantage over labelled diphosphonates for bone scan, used in the EU for the routine diagnostic work-up of prostate cancer, of targeting any location in a single test. The phase II studies confirmed that fluciclovine (^{18}F) PET-CT can identify areas of malignancy in the prostate and in extra-prostatic sites - lymph node metastases and bone metastases. Fluciclovine (^{18}F) has good imaging characteristics, with rapid uptake into malignant tissues. Moreover, the limited urinary excretion seems to be a further important advantage in comparison to fluorocholine (^{18}F).

Fluciclovine (^{18}F) has good imaging characteristics, with rapid uptake into malignant tissues. Moreover, the limited urinary excretion seems to be a further important advantage in comparison to fluorocholine (^{18}F). Nevertheless, comparative data versus fluorocholine (^{18}F) has not been provided.

As with every diagnostic method, PET imaging has clear limitations where fluciclovine (^{18}F) is not able to exclude with absolute certainty the presence of small volume recurrent micro-metastatic disease. The limited data available are, however, sufficient to show that fluciclovine (^{18}F) is a useful aid to the management of patients with biochemically suspected recurrent prostate cancer. Concerning the impact of fluciclovine (^{18}F) on patient management, the company has provided the full protocol of two ongoing company-sponsored studies, BED-003 and BED-004, in the intended clinical context and intended population and study results a be provided as soon as they are available.

3.8. Conclusions

The overall B/R of Axumin is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Axumin is favourable in the following indication:

"This medicinal product is for diagnostic use only.
Axumin is indicated for Positron Emission Tomography (PET) imaging to detect recurrence of prostate cancer in adult men with a suspected recurrence based on elevated blood prostate specific antigen (PSA) levels after primary curative treatment.
For the limitations in the interpretation of a positive scan, see section 4.4 and 5.1."

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 medical prescription.

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.

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

Risk Management Plan (RMP)

The 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 Axumin in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme with the National Competent Authority.

The MAH shall ensure that in each Member State where Axumin is marketed, all Healthcare professionals who are expected to use Axumin have access to self-training educational material in order to reduce the risk of PET imaging interpretation errors.

The Healthcare professionals self-training material shall contain the following key elements:

- Physiological distribution of fluciclovine
- Image interpretation guidelines
- Examples of incidental findings on PET-CT with fluciclovine
- Examples of positive and negative findings on PET-CT with fluciclovine
- Self-assessment test case images obtained with fluciclovine and expert summary for self-marking

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

Not applicable.

New Active Substance Status

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