14 September 2017
EMA/644309/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TOOKAD

International non-proprietary name: padeliporfin

Procedure No. EMEA/H/C/004182/0000

Note

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

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List of abbreviations

AE	adverse event
ANCOVA	analysis of covariance
5-ARI	5-α-reductase inhibitor
Bpheide	Bacteriopheophorbicide A
CE	Conformité Européene (European Conformity)
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CPP	Critical process parameter
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTGC	Central Treatment Guidance Committee
DRE	digital rectal examination
DSMB	Data Safety Monitoring Board
EC	European Commission
ECG	electrocardiogram
EMA	European Medicines Agency
EPN	Extra-prostatic necrosis
EQ-5D	EuroQol-5D
5-ARI	5-α-reductase inhibitor
EU	European Union
GC	Gas Chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good manufacturing practice
HPLC	High performance liquid chromatography
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-OES	Inductively coupled plasma-optical emission spectrometry
IEC	Independent Ethics Committee
IIEF-15	International Index of Erectile Function – 15 Questions
IPC	In-process control
IPSS	International Prostate Symptom Score
ITT	intention-to-treat
IV	intravenous
KF	Karl Fischer titration
LDI	light density index
LOQ	limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat

mpMRI	multiparametric magnetic resonance imaging
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NMT	not more than
NO	nitrogen oxide
NOAEL	No observed adverse effect level
NOEL	No Observed Effects Level
ORP	Outcomes Review Panel
PBT	persistent, bioaccumulating or toxic
Pd-Bchl-D	palladium-coupled bacteriochlorophyll derivative
PDT	photodynamic therapy
PEC	Predicted Environmental Concentration
PES	Polyethylsulfone
Ph. Eur.	European Pharmacopoeia
PIF	photo-irritancy factor
PK	Pharmacokinetic
PP	per-protocol
ppm	Parts per million
PT	preferred term
PSA	prostate-specific antigen
PTFE	Polytetrafluoroethylene
QoL	quality of life
Q1	first quartile
Q3	third quartile
RH	Relative Humidity
ROS	Reactive oxygen species
rpm	Revolutions per minute
RR	risk ratio
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	Standard Operating Procedure
TNM	tumour, nodes, metastasis
TURP	transurethral prostate resection
TRUS	transrectal ultrasound
UV	ultraviolet
VAS	visual analogue scale
VTP	vascular-targeted photodynamic therapy
WFI	Water for injections

1. Background information on the procedure

1.1. Submission of the dossier

The applicant STEBA Biotech S.A submitted on 7 January 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Tookad, through the centralised procedure falling within the Article 3(1) and point 3 of Annex 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:

Tookad is indicated for the treatment of low-risk localised prostate cancer.

Tookad is indicated in adult males.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that padeliporfin 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 CW/1/2011 on the granting of a class waiver.

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 padeliporfin 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 / Protocol Assistance

The applicant received Scientific Advice from the CHMP on 21 June 2007 and on 16 December 2010. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Bruno Sepodes Co-Rapporteur: Greg Markey

- The application was received by the EMA on 7 January 2016.
- The procedure started on 28 January 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 22 April 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 April 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 April 2016.
- During the meeting on 26 May 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 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 and 29 November 2016.
- During the PRAC meeting on 1 December 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 15 December 2016, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 March 2017.
- During a meeting of a SAG on 4 April 2017, experts were convened to address questions raised by the CHMP.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 11 April 2017.
- During the CHMP meeting on 21 April 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 18-21 April 2017, the CHMP agreed on a 2nd list of outstanding issues to be addressed by the applicant which was adopted via written procedure on 28 April 2017.
- The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on 20 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 3 July and 14 July 2017.
- During the PRAC meeting on 6 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.

- During the CHMP meeting on 20 July 2017, the CHMP agreed on a 3rd list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the 3rd CHMP List of Outstanding Issues on 11 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 3rd List of Outstanding Issues to all CHMP members on 23 August and 8 September 2017.
- During the PRAC meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 11-14 September 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 Tookad on 14 September 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Tookad is indicated as monotherapy for adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and:

- Clinical stage T1c or T2a,
- Gleason Score ≤ 6, based on high-resolution biopsy strategies,
- PSA ≤ 10 ng/mL,
- 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1 -2 positive cancer cores with ≥ 50 % cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/cm^3.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Prostate cancer is the second most common cancer in men. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759,000) occurring in more developed regions. In 2012, 420000 new cases were diagnosed and 101000 deaths estimated in Europe (Globocan, 2012).

The risk of clinically significant prostate cancer is related to age, ethnicity, family history, PSA level, free/total PSA ratio and findings on digital rectal examination (DRE) (Thompson IM, et al. 2006).

The use of prostate-specific antigen (PSA) testing has enabled detection stage of prostate cancer at earlier stages, resulting in increased diagnosis rates (Neppl-Huber, Zappa et al. 2012).

Based on a study in Spain, about 90% of the newly diagnosed cases of prostate cancer are localised, while the remaining 10% include locally advanced and metastatic forms (Cózar JM et al. BJU Int. 2012). Localised prostate cancer is defined as stage T1/T2, Nx/N0, M0.

2.1.3. Clinical presentation, diagnosis and stage / prognosis

Localised prostate cancer (stage T1/T2, Nx/N0, M0) is classified as low-, intermediate- or high-risk as a guide to prognosis and therapy (ESMO guideline). Among new cases of localised prostate cancer, many men (42%) exhibit a low risk profile, defined as T1c/T2a, prostate specific antigen 10 ng/ml or less, and Gleason score 6 or less (D'Amico, Whittington et al. 1998). Among these patients, some are considered very low-risk, defined as: stage T1c, Gleason score ≤ 6, 1 or 2 positive prostate biopsy cores, PSA density ≤ 0.15 ng/mL/cm^3 and < 50 % cancer involvement in each core.

When the cancer is confined to the prostate gland, median survival in excess of 5 years can be anticipated (Andriole GL, et al, N Engl J Med 2009).

2.1.4. Management

There is no consensus regarding optimum management of localised disease. Watchful waiting with delayed hormone therapy for symptomatic progression is an option for men who are not suitable for, or unwilling to have, treatment with curative intent.

Four primary therapeutic strategies are recommended for patients exhibiting a low risk profile: active surveillance, brachytherapy, radical prostatectomy, radical radiotherapy (ESMO clinical practice guideline, July 2015).

Active surveillance is a strategy of close monitoring, typically using serum PSA, repeat prostate biopsies and/or MRI, keeping curative treatment in reserve for those with early evidence of disease progression. It aims to achieve the correct timing for curative treatment in patients with a life expectancy over 10 years through a predefined schedule. The choice of deferred treatment depends on the treatment intent (curative vs. palliative) and life expectancy. Suitable patients must be fully apprised of surgery and radiotherapy options and counselled on the possibility of requiring further treatment in the future. Studies have shown that among low risk patients on active surveillance, 4 to 10% progress to active treatment at 1 year and 15 to 27% progress at 2 years.

Active surveillance and deferred treatment of localised prostate cancer (stage T1/T2, Nx/N0, M0) has been associated with case-specific survival at 10 years between 96%-100% (Mottet et al., European Association of Urology 2015).

For radical treatments for low risk prostate cancer the case specific survival at 10 years and recurrence free survival are very high. Patients with low risk prostate cancer who are unwilling to pursue active surveillance receive radical treatment. These interventions all have side effects, mainly local bladder, bowel and sexual dysfunction. Problems include erectile dysfunction in 30-90%, urinary incontinence in 5-35% and rectal symptoms in 1-11% of treated patients. The decision to proceed with radical treatment is based on assessment of the probabilities of clinical progression, side-effects and potential survival benefit.

Focal ablative therapies as cryotherapy and high intensity focused ultrasound (HIFU) are recommended in European guidelines only as alternative therapeutic options for low risk patients who are unfit for surgery or radiotherapy.

About the product

Tookad (padeliporfin) is palladium bacteriopheophorbide monolysotaurine, also known as padeliporfin-di-potassium or WST11. It is a derivative of bacteriochlorophyll, the photosynthetic pigment of certain aquatic

bacteria that draw their energy supply from sunlight, and becomes pharmaceutically active when illuminated by light. The UV / visible spectrum of the drug product in plasma present 5 maxima at 276 nm - 334 nm - 384 nm - 518 nm and 753nm, with a peak of absorption in the near-infrared wavelengths at ~ 753 nm.

Tookad vascular targeted photodynamic therapy (VTP) consists of intravenous administration of Tookad, followed immediately by local activation by low – energy laser light illumination.

Padeliporfin is retained within the vascular system. When activated with 753 nm wavelength laser light, padeliporfin triggers a cascade of pathophysiological events resulting in focal necrosis within a few days. Activation within the illuminated tumour vasculature, generates oxygen radicals (•OH, $O_2^{\bullet-}$) causing local hypoxia that induces the release of nitric oxide (•NO) radicals. This results in transient arterial vasodilatation that triggers the release of the vasoconstrictor, endothelin-1. Rapid consumption of the •NO radicals, by oxygen radicals, leads to the formation of reactive nitrogen species (RNS) (e.g. peroxynitrite), in parallel to arterial constriction. In addition, impaired deformability is thought to enhance erythrocyte aggregability and formation of blood clots at the interface of the arterial supply (feeding arteries) and tumour microcirculation, results in occlusion of the tumour vasculature. This is enhanced by RNS-induced endothelial cell apoptosis and initiation of self-propagated tumour cells necrosis through peroxidation of their membrane (see SmPC section 5.1).

The initially claimed indication was for treatment of low-risk localised prostate cancer in adult males.

The approved indication is:

Tookad is indicated as monotherapy for adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and:

- Clinical stage T1c or T2a,
- Gleason Score ≤ 6, based on high-resolution biopsy strategies,
- PSA ≤ 10 ng/mL,
- 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1 -2 positive cancer cores with ≥ 50 % cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/cm^3.

Tookad is restricted to hospital use only. It should only be used by personnel trained in the Vascular-Targeted Photodynamic therapy (VTP) procedure (see SmPC section 4.2).

The recommended posology of Tookad is one single dose of 3.66 mg/kg of padeliporfin.

Tookad is administered as part of focal VTP. The VTP procedure is performed under general anaesthetic after rectal preparation. Prophylactic antibiotics and alpha-blockers may be prescribed at the physician's discretion.

Retreatment of the same lobe or sequential treatment of the contralateral lobe of the prostate are not recommended (see section 4.4).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for solution for injection containing 183 or 366 mg of padeliporfin (as its dipotassium salt) as active substance.

The only other ingredient is mannitol.

The product is available in amber type I glass vials sealed rubber stoppers crimped with aluminium seals and covered with blue plastic flip-off caps, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of padeliporfin dipotassium is palladate(2-), [(7*S*,8*S*,17*R*,18*R*)-13-acetyl-18-ethyl-5-(2-methoxy-2-oxoethyl)-2,8,12,17-tetramethyl-3-[[(2-sulfoethyl)amino]carbonyl]-21*H*,23*H*-porphine-7-propanoato(4-)-κ*N*21,κ*N*22,κ*N*23,κ*N*24]-dipotassium corresponding to the molecular formula $C_{37}H_{41}K_2N_5O_9PdS$. It has a relative molecular mass of 916.4 g/mol and the following structure (Figure 1).

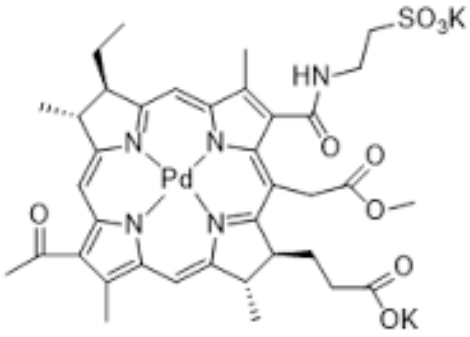


Figure 1 Structure of padeliporfin dipotassium

The chemical structure of padeliporfin dipotassium was elucidated by a combination of ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, mass spectrometry, elemental analysis, ultraviolet spectroscopy and infrared spectroscopy.

The active substance is a very hygroscopic dark powder, soluble in aqueous media and practically insoluble in most organic solvents. Polymorphism is not considered important for padeliporphin as it is dissolved during formulation and subsequently freeze-dried. Its aqueous solubility is ideally suited to the reconstitution operation ahead of injection.

Padeliporphin contains four chiral centres. All stereocentres originate in the fermentation step and are derived from enzymatic processes within the organism. Optical rotation measurements on the active substance have shown that a single enantiomer is routinely produced. Accordingly, no test for enantiomeric purity is deemed necessary in the active substance specification.

Manufacture, characterisation and process controls

The active substance is synthesized in three main steps from two starting materials. During the procedure, a major objection was raised, requesting re-definition of one of the starting materials. CHMP considered that not enough of the process was included in the process description, and that an additional upstream step needed to to documented in the dossier and carried out under GMP to ensure the quality of the active substance throughout its life cycle. The applicant was able to re-define one of the starting materials, thus resolving the issue.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Only minor changes have been made to the process, including changes of solvent for

purification processes and transfer of the process to a new manufacturer and subsequent scale up. These changes resulted in a higher quality active substance.

Adequate in-process controls are applied during the synthesis. Critical process parameters (CPPs) have been defined for each step of the process to ensure adequate conversion and selectivity. 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 active substance is packaged in type I amber glass bottles, with high hydrolytic resistance and polysulfone (PSU) screw caps with double sided polytetrafluoroethylene (PTFE) protected silicon seals which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. This container closure system was chosen as the best primary packaging option due to the sensitivity of the active substance to light, oxygen and humidity.

Specification

The active substance specification (see table below) includes tests for appearance, identification (UV, HPLC), assay (HPLC), purity (HPLC and GC), residual solvents (GC), water content (KF), free palladium (HPLC of derivatized Pd), pH, and microbial control (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. A chromatographic test method for free palladium was introduced as it has a lower LoQ compared to the previous ICP-OES method.

The control strategy ensures production of the correct stereoisomer and so no test for enantiomeric purity is deemed necessary in the active substance specification.

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 for assay and impurities testing has been presented.

Analysis data from three production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch. Additional impurity data from batches used in toxicology studies were also provided in order to justify the impurity limits in the proposed specification.

Stability

Stability data on 9 pilot to production scale batches of active substance from the proposed manufacturer and 3 from a previous manufacturer stored in the intended commercial package for up to 60 months under long term conditions (-20 ºC) according to the ICH guidelines were provided. Data from 6 of the batches, including 3 from the previous manufacturer, stored in the intended commercial package for up to 6 months under accelerated conditions (5 ºC) were also provided. Samples were tested for appearance, assay, purity and water content. The analytical methods used were the same as for release. No significant changes to any of the measured parameters were observed and all remained within specification at each time point. Water content fluctuated more than other parameters due to the hygroscopic nature of the active substance.

Photostability testing following the ICH guideline Q1B was performed on one batch resulting in significant degradation indicating that padeliporfin is photosensitive.

Forced degradation studies were carried out under the following conditions: heat (110 ^{o}C); heat and humidity (60 ^{o}C / 100% RH); acid (0.1M HCl, 60 ^{o}C); base (0.1M NaOH, 60 ^{o}C); oxidant (H_2O_2, room temperature). Samples degraded under all conditions and it was demonstrated that the analytical methods are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months at -20 ^{o}C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a lyophilized powder for reconstitution in 5% glucose solution and subsequent injection. Two strengths are available containing 200 or 400 mg of the active substance, equivalent to 183 or 366 mg of padeliporfin free base.

The aim was to develop a stable formulation of paedliporfin dipotassium. The active substance becomes pharmaceutically active on exposure to light of the correct wavelength and must thus be protected from light during formulation and storage. It is soluble in aqueous media and sensitive to heat and oxygen. Solid formulations were found to be more stable than solutions and so a lyophilised formulation which would dissolve rapidly on addition of an aqueous reconstitution liquid to afford a solution of suitable pH for injection was sought.

Mannitol was found to be the best bulking agent of those investigated, affording a stable lyophilisate and improving the hydrophilicity of the formulation, thereby increasing its speed of dissolution. It is the sole excipient, a well known pharmaceutical ingredient and its 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. Water for injections (WFI) is the chosen solvent and is removed during freeze drying.

All processing is carried out under a nitrogen atmosphere to avoid oxidative degradation and under filtered light, to avoid photodegradation. Temperature and time of individual steps are limited to avoid degradation.

The lyophilisation process was optimised to ensure a suitable cake with low moisture content. Parameters for freezing as well as primary and secondary drying have been defined.

Due to the heat-sensitivity of the active substance, terminal sterilisation is not possible. Therefore, sterility is ensured by sterile filtration followed by aseptic filling and lyophilisation. Leachable studies have demonstrated compatibility with the filters and lyophilisation kit which covers the proposed processing time.

Leachable studies were also conducted with the injection kit which is opaque to prevent photodegradation. The finished product, reconstituted to 9.15 mg/ml padeliporfin in 5% glucose was found to be stable for up to 2 hours. Suitable reconstitution instructions are found in the SmPC, section 6.6.

The primary packaging is an amber type 1 glass vial sealed with a rubber stopper crimped with an aluminium seal and covered with a plastic flip-off cap. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The hermetically sealed container has been shown to maintain sterility throughout the proposed shelf life.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: formulation; pre-filtration; sterile filtration; aseptic filling; lyophilisation; capping. The process is considered to be a non-standard manufacturing process.

The pre-filtration step is followed by a bioburden test to ensure a sufficiently low level of bioburden (<10 CFU/100 ml) prior to sterile filtration. Following sterile filtration, each filter is tested for integrity using the bubble point method. A sterility test is subsequently performed on a sample prior to aseptic filling. Following stoppering and capping, a hermeticity test is performed to ensure appropriate sealing and maintenance of sterility.

The critical steps of the manufacturing process have been validated on three consecutive production scale batches of each strength. The process was also validated on 3 pilot scale batches of the 183 mg strength. 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 and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identification (UV, HPLC), content (HPLC), impurities (HPLC), water content (KF), average mass (Ph. Eur.), uniformity of mass (Ph. Eur.), particulate contamination (Ph. Eur.), reconstitution (visual), pH and osmolarity of reconstituted solution (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

No new degradants are formed during finished product manufacture. All impurities are already limited in the active substance specification. Limits set are in line with the amounts qualified in toxicology and clinical studies.

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 assay and impurities testing has been presented.

Batch analysis results are provided for eight pilot to 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 from 16 pilot to commercial scale batches of finished product including 7 from the original manufacturer of clinical material and 9 from the proposed commercial manufacturer (of which 3 of each strength were manufactured on commercial scale) were provided. Samples were stored for up to 60 months under long term conditions (5±3 ^{o}C) and for up to 6 months under accelerated conditions (25 ^{o}C / 60% RH) according to the ICH guidelines. Studies using batches from the proposed commercial manufacturer under long term conditions have been conducted up to 36 months only but the batches from the previous manufacturer are considered representative. The batches were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, pH of reconstituted solution, identity, assay, impurities and reconstitution. Particulate contamination, sterility and bacterial endotoxin tests are performed at the start and end of each stability study. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters were observed throughout the studies.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed. When stored in a clear glass vial however, some degradation occurred. This indicates that the finished product is photosensitive but that the amber vial provides sufficient protection.

A second photostability study was undertaken using the reconstituted solution in the injection kit. Slight degradation was observed in the clear kit after 110 minutes, although impurities were well within specification. The higher the intensity of light used, the faster the degradation. It is therefore recommended to use opaque injection kit where the light intensity in the operating room can't be controlled.

An in-use stability study was conducted with the reconstituted finished product to evaluate short term stability in the original container and in the injection kit. A slight increase in one impurity was observed at room temperature and under refrigerated conditions in the presence of yellow light, though the level was within specification limits. It is concluded that the reconstituted product remains stable for up to 8 hours. The study was repeated in the opaque injection kit, stored at room temperature under yellow light for up to 2 hours. Although an increase in the same impurity was observed, results remained within specification. In-use shelf lives are reported in the SmPC, section 6.3 although from a microbiological point of view, immediate use is recommended.

Based on available stability data, the proposed shelf-life of 60 months stored in a refrigerator (5±3 ^{o}C) in the outer carton to protect from light as stated in the SmPC (section 6.3) is 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 and finished product has been presented in a satisfactory manner. The limits for impurities have been justified in line with qualified levels. The process has been fully validated and it has been shown to provide a sterile finished product suitable for injection. Suitable instructions for reconstitution, including how to protect from light, have been provided. 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 product information (SmPC and PIL). 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. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical studies were conducted according to GLP with some exception of auxiliary parts of the main studies. The core safety pharmacology studies were conducted according to GLP.

The pharmacology package consisted of pharmacodynamic studies in a variety of animal cancer models - prostate cancer, cholangiocarcinoma, non-small cell lung cancer and renal cancer, with studies completed using dogs and pigs. A safety pharmacology programme was conducted to explore effects of the central nervous system (CNS) and respiratory system and coagulation. In terms of cardiovascular safety, three safety pharmacology studies were conducted.

The general toxicology programme consisted of single and repeat dose toxicity studies in the mouse, rat and *Cynomolgus* monkey. Each study was completed using intravenous administered WST11 (padeliporfin), the clinical route of administration. A full range of genotoxicity and photo-genotoxicity studies have been completed, alongside local tolerance and antigenicity studies. Reproductive toxicity and carcinogenicity studies were not submitted.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Table 1 In vivo pharmacodynamic studies with padeliporfin (WST11)

Type of Study	Test System	Method of Administration	Sponsor Study No. (Test Facility Study No.)
Efficacy and Tolerance	Normal canine prostate (mongrel dogs)	iv, by infusion pump	PLG/MLT 071294S PREC 0806 PDM
Safety and Efficacy	Normal canine prostate (beagle dogs)	iv, by infusion pump	STEBA 08-06
Efficacy and Tolerance of Tookad, Stakel and LC45/WST09	Pig biliary and peribiliary tissues (Large White x Landrace x Pietrain mixed breed)	iv, by infusion syringe pump	NEGMA 07-14 PLG/WST 07 1293N

Effect on Lung Tissue During PDT Using WST11	Pig lung (mixed White x Landrace)	iv , by infusion syringe pump	STEBA 08-01
Effects on Renal tissue during VTP using WST11	Healthy pigs (four and a half to five month-old)	iv , by infusion syringe pump	STEBA 10-21

Results from studies STEBA 10-21, STEBA 08-01 and NEGMA 07-14 are not presented in details as not performed in prostate tissue.

Efficacy and tolerance of WST11 in the normal canine prostate (Study No. PREC 0806 PDM)

The aim of this study was to evaluate the dose escalating effect of a 10-minute i.v. infusion of WST11 followed by light-activation with a 753 nm diode laser (WST11 - VTP therapy) on the normal prostate of old mongrel dogs, using different light fluence rates. Several drug doses and illumination conditions were used to assess the efficacy of WST11 - VTP in inducing the necrotic ablation of the prostate: drug doses of 1.0; 2.0; 5.0; 7.5; 10 and 15 mg/Kg, coupled with 100 to 400 J/cm of fibre (one light dose/prostate lobe). In WST11-mediated VTP, the coupling of a drug dose of 2.0 mg/kg together with a light-dose of 200 J/cm of fibre was shown to safely induce necrosis of the targeted prostate tissue in the normal dog.

Effect on Prostatic Tissue During PDT Using WST11 and WST09 (Study No. STEBA 08-06)

The aim of this study was to evaluate the safety and efficacy of WST09 (padoporfin, a predecessor molecule) and WST11 in prostatic tissues.

Additionally, pharmacokinetic dosages and other safety parameters were assessed over 24 hours post injection. This prospective study included 12 animals, 3 groups, one group of 4 animals administered WST09 at the dose of 2 mg/kg, one group of 2 animals administered WST11 at 2mg/kg and one group of 6 animals administered WST11 at 5 mg/kg. There were no undue safety issues revealed by the study. Animals recovered safely from surgery. Main conclusions in terms of efficacy are the following: WST09 and WST11 with appropriate laser energy induced massive haemorrhagic necrosis of prostatic parenchyma in the normal dog. The prostatic capsule was also affected, although this could easily be explained by the proximity between the fibres and the capsule, due to the relatively small size of the canine prostates.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were provided (see discussion on non-clinical aspects).

Safety pharmacology programme

Table 2 Summary of safety pharmacology data from studies performed with WST11

Organ Systems Evaluated	Species/ Strain	Dosing Method	Doses (mg/kg)	Gender and nº per Group	Noteworthy Findings	GLP	Sponsor Study No. (Test Facility Study No.)
Central Nervous	Wistar rat	iv	50, 100, 150	4 M	50, 100, and 150 mg/kg: no effect on behavior and physiological function and absence of toxicity.	GLP	PLG/MLT 03660N (03.294/3)
Cardiovascular (hERG)	Human embryonic kidney cell (hERG transfected)	in vitro	0.1, 0.3, 1, 3, 10, 30 µM	5–7 cells	0.1 to 30 µM: weakly blocked hERG current amplitude at 0.1 Hz, failing to produce greater than a 20% mean inhibition of hERG current at highest concentration tested (30 µM). This leads to a very low liability for prolonging QT.	Non-GLP**Footnote 1*	PLG/MLT 03661N (03.296/3)

Cardiovascular (BP, heart rate, and ECG)	Cynomolgus monkey	iv	Parts I and III: Vehicle (5% glucose) – 20 mL/kg 25 (5 mg/mL; 1.5-2 mL/min) 50 (5 mg/mL; 3-4 mL/min) 100 (5 mg/mL; 6-8 mL/min) Part IV: Vehicle (5% glucose + mannitol) 20 (10 mg/ml; 16 mL/min) 25 (10 mg/mL; 16 mL/min) 50 (10 mg/mL; 8, 16, and 20 mL/min)	6 M	**In conscious animals (Part I)**: No effect on cardiovascular function. NOAEL: 50 mg/kg. **In anaesthetized animals (Part III)**: 50 and 100 mg/kg: a slight statistically significant reduction of the hypertension seen in the control group, associated with a bradycardia. 25, 50, and 100 mg/kg: prolongation of ventricular depolarization associated with a decreased atrio-ventricular depolarization rate at 100 mg/kg only. NOAEL: not achieved. **In anaesthetized and conscious animals**: Vomiting observed at 100 mg/kg. **Complementary investigations in conscious animals (Part IV)**: Tendency to a bradycardia at all dose- levels 50 mg/kg (8, 16, and 20 mL/min) and 25 and 20 mg/kg (16 mL/min) associated with hypotension at 50 mg/kg (20 mL/min). NOAEL: 25 mg/kg at 16 mL/min.	GLP	PLG/MLT 03671N (CERB 20030481PCCY)
Cardiovascular (BP, heart rate, body temperature, and ECG)	Anaesthetized monkeys (second study 2009)	iv	25,50 and 100 (5 mg/ml; maximal duration of dosing: 10 minutes)	5M	At 25 and 50 mg/kg: no statistically significant changes in cardiovascular parameters. At 100 mg/kg: during anaesthesia, slight, non-statistically significant decrease in heart rate and consequently slight increase on the QT interval (statistically significant from 0.5 to 1 hour post- dosing); no change in QTc calculated by Bazett's formula, by the probabilistic method or by the QT shift. NOAEL: close to 100 mg/kg.	GLP	CERB Study n° 20090152PCCYPB
Respiratory	Wistar rat	iv	50, 100, 150	8 M	50 and 100 mg/kg: no effect on any of the nine respiratory parameters evaluated in conscious rat. 150 mg/kg: slightly and transiently decreased pause from 30 min following administration.	GLP	PLG/MLT 03662N (03.297/3)
Coagulation	Wistar rat	iv	50, 100, 150	8 M	50, 100, and 150 mg/kg: no effect on bleeding time.	GLP	PLG/MLT 03663N (03.298/3)

Pharmacodynamic drug interactions

No studies were provided which was considered acceptable (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

No absorption data were submitted because WST11 is only administered by the intravenous route. Distribution studies were characterised in a single rat biodistribution study, and with distribution to blood and plasma. WST11 concentrations were determined in pharmacokinetic and toxicokinetic samples. Metabolic studies were limited to examination in human liver microsomes. Elimination and potential drug interactions with WST11 were not provided (see discussion on non-clinical aspects).

Table 3 Overview of Pharmacokinetic Parameters in Single and Repeated Dose Studies

Assessment Time	Dosage (mg/kg/day)	Cmax (µg/mL)		AUC	
		Male	Female	Male	Female
Quantitative Tissue Distribution After Single-Dose Administration in Sprague-Dawley Rats (PKH/MLT 03672N)					
Plasma	10	101.54[a]	NA	29.77[b]	NA
Liver	10	63.90[a]	NA	14.8[b]	NA
4 Week Intravenous Toxicity Study in Sprague-Dawley Rats (758/034)					
Day 0	25	264	210	78.4[c]	61.7[c]
	75	553	546	265[c]	226[c]
	150	733	933	845[c]	866[c]
Day 27	25	226	198	67.6[c]	58.2[c]
	75	555	598	261[c]	265[c]
	150	897	1000	696[c]	687[c]
7 Day Intravenous Dose-Ranging and Toxicity Study in Cynomolgus Monkeys (758/035)					
Day 0	50	656	312	603.34[d]	206.56[d]
	100	1200	987	2168.69[d]	1254.54[d]
	150	1570	1470	4538.90[d]	3372.69[d]
Day 6	50	748	460	761.53[d]	350.66[d]
	100	1230	810	2165.01[d]	1136.37[d]
	150	1510	1430	3627.85[d]	3020.70[d]
2 Week Intravenous Toxicity Study in Cynomolgus Monkeys – Mean ± SD (Study 758/036)					
Day 0	25	385 (16.20)	375 (63.65)	235.49 (58.74)[d]	161.37 (68.78)[d]
	100	1177 (152)	1123 (46.19)	2198.55 (50.11)[d]	1632.81 (342.89)[d]
	150	1670 (123)	1597 (132)	3237.44 (357.86)[d]	3757.96 (804.75)[d]
Day 13	25	372 (16.80)	408 (46.70)	220.32 (75.71)[d]	161.49 (26.37)[d]
	100	1403 (328)	1102 (118)	2179.96 (150.51)[d]	2172.39 (975.08)[d]
	150	1463 (127)	1733 (110)	2399.54 (1099.03)[c]	3278.89 (836.41)[c]

[a] = C_{max} (nmol/L plasma or nmol/g liver).

[b] = AUC_{inf} (nmol·h/mL plasma or nmol·h/g liver).

[c] = AUC_{0-4h} (µg·h/mL).

[d] = AUC_{0-t} (µg·h/mL).

Distribution

The distribution of WST11 was studied following a single intravenous dose of 10 mg/kg in male Sprague-Dawley rats (Report PKH/MLT 03672 N, GLP). WST11 was quantified in plasma, blood cells, eyes, bone, fat, liver, lung, skin, kidneys, and muscle. The concentration of WST11 in eyes, fat, skin, and muscle were below the LOQ for all the time points. At 4 h postdose, the concentration of WST11 was below the LOQ for all the tissues.

Measurable concentrations of WST11 were observed only in the first few sampling times of plasma, blood cells, liver, lung, and kidneys. Maximum concentrations of WST11 were observed in plasma and liver, and elimination was rapid. The maximum recovery was observed in liver and represented 26% of the administered dose at the first sampling time. The amount decreased rapidly and was below 2% 1 h after dosing. A low concentration of WST11 was observed in the eyes and skin, which may suggest a low probability of phototoxicity. There was little to no distribution of WST11 to skin tissue or to the rat eye at any time-point, from 2 minutes to 168 hours post-dose.

The *in vitro* partitioning of WST11 between the cellular-fraction and the plasma-fraction of whole blood was evaluated (Report PKH/MLT 04691N, non GLP). Human blood obtained from one healthy volunteer was collected using lithium heparinate as anticoagulant.

The distribution of the WST11 between blood cells and buffer was first carried out in order to determine the binding capacity of blood cells. Afterwards, the distribution of WST11 added to whole blood was measured in the cellular fraction and in plasma in order to determine the retentional effect of plasma. No significant binding of WST11 to the cellular fraction occurred in presence of blood plasma. These results indicated that WST11 has a higher affinity for the plasma fraction, perhaps plasma protein, than for blood cells.

These results correlated with those previously presented in the study (Study HPC/MLT 02 655N/MLT 1.01 in which human blood samples were obtained from 1 male/female healthy volunteer and binding to human plasma proteins determined using equilibrium dialysis and the blood partitioning methodology), which showed that a high percentage of WST11 (98.97 %) was bound to plasma proteins.

Metabolism

Three *in vitro* biotransformation studies were performed with WST11, two with human liver microsomes Study 9977, non-GLP and Study 10941/TL, non-GLP), and a third with human liver S9 fractions (Study 11258/ PKH/MLT 051274N, GLP). WST11 was incubated with liver microsomes for 60 minutes and the mean percentage of parent remaining was 89% (1 µM) and 97% (10 µM). WST11 was also found 90% unchanged when incubated with liver S9 fractions. WST11 was found unchanged after 60 min incubation. No metabolite from Phase I or Phase II was found.

Excretion

No specific studies were conducted to study excretion of WST11. The elimination of WST11 was assessed in the quantitative tissue distribution study (Report PKH/MLT 03672 N) of WST11 administered to rats. The detection of WST11 in the urine and faeces of three individual rats over the 96 h post-dose period. The urinary excretion of WST11 is minimal, and that excretion is achieved primarily through fecal elimination after biliary excretion. This data is limited to sampling from 3 individual rats, with total recovery in the range of 41.5% to 96.4%.

2.3.4. Toxicology

Single dose toxicity

Table 4 Summary of single dose toxicity studies with WST11

Study ID	Species / Sex / Number / Group	Dose / Route	Observed max non-lethal dose	Major findings
MDS 758/024 GLP	OF1 Mouse/ 3/sex/group	0, 100, 200, 400 mg/kg IV	400 mg/kg	No deaths; Clinical signs were wounds and crusts on tails of males in 200 mg/kg group. No obvious signs of toxicity up to 400 mg/kg.
MDS 758/032 GLP	CD1 Mouse 5/sex/group	Main: 0, 100, 200, 300 mg/kg IV	100 mg/kg	9 deaths: 2M@200 mg/kg; 5M & 2F@300 mg/kg Clinical signs at 200 and 300 mg/kg; convulsions, red-coloured teguments, purple-red coloured faeces, piloerection, and/or subdued behaviour. NOEL: 100 mg/kg
MDS 758/031 GLP	Sprague Dawley Rat 5/sex/group	Main: 0, 100, 200, 300 mg/kg IV	200 mg/kg	3 deaths: 3F at 300 mg/kg Clinical signs at 200 and 300 mg/kg of piloerection and subdued behaviour; NOEL: 100 mg/kg

MDS 758/041 GLP	Sprague Dawley Rat 5/sex/group	0, 150, 300 mg/kg IV	300 mg/kg	No deaths; Clinical signs at 150 and 300 mg/kg of subdued behaviour, red-coloured teguments, half-closed eyes, purplish urine, laboured breathing, piloerection at 300 mg/kg.

M=male; F=female; NOEL=No Observed Effects Level

Repeat dose toxicity

Table 5 Summary of repeated dose toxicity studies with WST11

Study ID	Species/Sex/ Number/ Group	Dose/Route	Duration	NOAEL (mg/kg/ day)	Major findings
MDS 758/033 GLP DRF	Sprague Dawley Rat 5/sex/group	0, 50, 100, 150 IV	7 days	ND MTD=150	No deaths Liver (no relevant microscopic lesions or macroscopic findings). No signs of systemic toxicity, change in body weight, organ weight or in haematological and blood biochemical parameters.
MDS 758/034 GLP Pivotal	Sprague Dawley Rat 10/sex/group 5/sex/group (recovery)	0, 25, 75, 150 IV	28 days	150	<u>150 mg/kg/day:</u> Mortality: 1M death – cause unknown but assumed related to procedure conditions. Clinical: Subdued behaviour Haem/biochemical: ↑reticular count in M&F; ↑prothrombin time 2F; ↓ASAT activity 4F Histopathological: ↓Liver weight in F <u>75 mg/kg/day:</u> Mortality: no deaths. Clinical: Subdued behaviour Haem/biochemical: ↑bilirubin 3M; ↑albumin 3M. Histopathological: ↓Thyroid weight in M <u>25 mg/kg/day:</u> No changes

MDS 758/035 GLP DRF	Cynomolgus monkey 1/sex/group	0, 50, 100, 150 IV	7 days	50	<u>150 mg/kg/day:</u> Mortality: no deaths Clinical: Coloured vomiting M&F 1 hr following treatment; dark, black and/or reddish faeces; injection site reactions Haem/biochemical: ↓RBC/Hb/PCV Histopathological: ↑Adrenal weight in M; dark areas in the colon; sinusoidal leucocytosis M&F <u>100 mg/kg/day:</u> Mortality: no deaths Clinical: red coloured vomit 1F a few minutes following treatment; dark, black and/or reddish faeces; injection site reactions. Haem/biochemical: ↓RBC/Hb/PCV Histopathological: ↑Adrenal weight in M; dark areas in the colon F; sinusoidal leucocytosis F. <u>50 mg/kg/day:</u> Mortality: no deaths Clinical: dark, black and/or reddish faeces; injection site reactions. Haem/biochemical: ↓RBC/Hb/PCV Histopathological: ↑Adrenal weight in M.

MDS 758/036 GLP Pivotal	Cynomolgus monkey 3-4/sex/group	0, 25, 100, 150 IV	14 days	25	<u>150 mg/kg/day:</u> Mortality: 1M and 2F. Male vomited in day 4, suffered prostration multiple occasions, subdued activity – ethically sacrificed. 1 female was prostrate and had severe sores on hindlimbs from day 7 – sacrificed due to suffering on day 13. Sores attributed to restraints used during dosing. 1 female sacrificed due to handling error where knee was dislocated. Clinical: emesis, prostration, reduced activity, and decreased food consumption; 1F had swollen face. Sores on legs. Pink-coloured faeces/urine. ↓Heart rate; injection site reactions Haem/biochemical: All M and 1F - regenerative anaemia, an increase in the APTT. ↑Bilirubin 1M. Histopathological: ↓Thymus weight in M; Joint lesions (arthritis and cartilaginous necrosis) in two animals <u>100 mg/kg/day:</u> Mortality: no deaths Clinical: decreased food consumption; 1F had swollen face; 1F swollen eyelids; Sores on legs. Pink-coloured faeces/urine. ↓Heart rate; injection site reactions. Haem/biochemical: None reported Histopathological: ↓Thymus weight in M; <u>25 mg/kg/day:</u> Mortality: no deaths Clinical: Sores on legs due to restraints. Pink-coloured faeces/urine; injection site reactions Haem/biochemical: None reported Histopathological: ↓Thymus weight in M;

DRF=dose range-finding; ND=not determined; MTD=maximum tolerated dose; NOAEL=No observed adverse effect level; APTT=activated partial thromboplastin time.

Genotoxicity

Table 6 Main results in genotoxicity studies

Test System	Species (Strain)/ Material	Metabolic Activation; UV Light	Maximal Tested Concentration/Dose	Result	Study No.
In Vitro Bacterial Reverse Mutation Test	*Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA102)	With and without S9; no UV exposure	Exp 1: 5000 µg/plate Exp 2: 5000 µg/plate, preincubation method	Negative	1750/5
	Salmonella typhimurium (TA98, TA100, TA1535, TA1537, TA102)	Without S9; with and without UV exposure	5000 µg/plate, plate incorporation method	Negative in both the presence and absence of UV light exposure	1750/6
In Vitro Chromosome Aberration Test	CHO (Chinese hamster ovary) cultured cell line	With and without UV exposure	Continuous (3 h) treatment (no S9) followed by 17 h recovery: up to 200 µg/mL Up to 6 µg/mL in the presence of 400 mJ/cm^2 and 800 mJ/cm^2 UV light exposure	Negative in the absence of UV light exposure Weak, but positive evidence of photo-clastogenic activity Effect was reduced when the UV dose was lowered by half when tested at the same concentrations	1750/7
	CHO (Chinese hamster ovary) cultured cell line	With and without S9; no UV exposure	Continuous (3 h) treatment (S9) followed by 17 h recovery: up to 2000 µg/mL Continuous (3 h) treatment (without S9) followed by 17 h recovery: up to 2000 µg/mL Continuous (20 h) treatment (without S9: up to 2000 µg/mL	Negative in both the presence and absence of S9 metabolic activation	1750/8

Carcinogenicity

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

Reproduction Toxicity

No reproductive and developmental toxicity studies were provided (see discussion on non-clinical aspects).

Examination of the effects of WST11 on male fertility and spermatogenesis has been provided by reviewing the effects on rat testes following repeated dose for 4 weeks with WST11. Histological examination of testes sections in the high dose group (150 mg/kg/day) did not reveal an effect on sperm cell population or an effect on any stage of spermatogenesis. The changes noted of seminiferous epithelial degeneration in a single high dose rat has been explained as related to the administration procedure, rather than treatment related. This animal also experienced an inflammatory lesion on the tail.

Toxicokinetic data

Table 7 Summary of repeated dose toxicokinetic studies

Study ID	**Daily Dose (mg/kg)**	**Animal AUC[1] (µg.h/ml)**		**Animal Cmax[2] (µg/ml)**		**Animal : Human Based on Cmax Exposure Multiple[3]**	
		Male	Female	Male	Female	Male	Female
28 day Sprague Dawley Rat	25	78.4	61.7	264	210	3.8	3.0
	75	265	226	533	546	7.6	7.8
MDS 758/034	**150 (NOAEL)**	**845**	**866**	**733**	**933**	**10.5**	**13.3**
7-day Cynomolgus monkey	**50 (NOAEL)**	**603**	**207**	**656**	**312**	**9.4**	**4.5**
	100	2169	1255	1200	987	*17.1*	*14.1*
MDS 758/035	150	4539	3373	1570	1470	*22.4*	*21.0*
14-day Cynomolgus monkey	**25 (NOAEL)**	**235**	**161**	**385**	**375**	**5.5**	**5.4**
	100	2198	1633	1177	1123	*16.8*	*16.0*
MDS 758/036	150	3237	3758	1670	1597	*23.9*	*22.8*

1=AUC0-4h at Day 0; 2=Cmax at Day 0; 3=Cmax 70 µg/ml after 4 mg/kg in humans (CLIN801 PCM201).

Local Tolerance

Local Tolerance in the Rabbit After Five Days, 20 mg/kg WST11 (Study CERB 20040101TL or PTH/MLT03669N, GLP)

Three groups of five female New Zealand albino rabbits were administered either WST11 at 20 mg/kg active ingredient, sterile and pyrogen-free isotonic saline solution control, or vehicle- control solutions by one daily intravenous injection for five days in the left ear, by intra-arterial injection on Day 5 in the right ear (WST11 20 mg/kg, saline, and vehicle at the same volume as WST11), and by perivenous injection on Day 5 in the right ear (WST11 0.5 mL, saline, and vehicle at the same volume as WST11). Injection site and macroscopic examination along with histopathology results were the main analyses in this study.

WST11, as administered in this study did not induce any clinical signs, and no local intolerability was attributed to WST11 after dosing by the intravenous, intra-arterial, or perivenous routes.

Other toxicity studies

Antigenicity

Antigenicity was studied in a single study to evaluate the potential of WST11 to induce immediate hypersensitivity in the male Hartley guinea pig after sensitisation by the subcutaneous or intravenous route (Study AA27635 or PLG/MLT 051262N, GLP). Animals were divided into 5 groups for both induction and for challenge phases, and were treated with 5 or 10 mg/mL WST11 via subcutaneous or intravenous routes (3 groups). A vehicle control group (mannitol in 5% glucose) and a positive control group (200 µg/mL ovalbumine) were also included.

Under the experimental conditions of this study, an intravenous challenge administration of WST11 at 10 mg/mL did not induce mortality or any signs of immediate hypersensitivity in animals sensitized by the subcutaneous or intravenous route at 5 or 10 mg/mL.

Studies on impurities

In silico qualitative evaluation of the potential carcinogenicity, chromosomes damages, genotoxicity and mutagenicity of 11 impurities was performed. None of the structure analysed triggered alerts for carcinogenicity, chromosome damage, genotoxicity and mutagenicity.

Blood Compatibility

In Vitro Blood Compatibility (Study PLG/MLT 03670N, or MDS AA18401, GLP)

This study was conducted in order to establish the compatibility of the WST11 formulation and vehicle with whole blood and plasma from rats, monkeys, and humans. WST11 was prepared as a solution at 5 mg/mL in the vehicle (3.34 mg/mL mannitol in 5% glucose). Saline (0.9% NaCl solution) and water for injection were used as negative and positive controls, respectively. Each test solution (WST11, vehicle, negative, and positive controls) was mixed with whole blood (obtained from male and female subjects from each species) in a 1:5 ratio.

WST11 at a concentration of 5 mg/mL had no effect on erythrocyte clumping and induce precipitation in rat, monkey or human blood. Due to the colour of WST11 solution, the evaluation of the haemolytic potential of WST11 was not possible in this study.

In Vitro Blood Compatibility (Study Ricerca Biosciences/ AA92816, GLP)

This second *in vitro* blood compatibility study was performed with a solution at 10 mg/mL in the same vehicle (6.67 mg/mL mannitol in 5% glucose) and performed according to a similar study design of the previous study, with the exception that saponin solution (3% w/v) was used in place of water.

There was no erythrocyte clumping, no precipitate and no sign of haemolysis. The review of haemolysis however was limited due to the colour of the WST11 solution.

Phototoxicity

Neutral Red Uptake Phototoxicity Assay of WST11 in Balb/c 3T3 Mouse Fibroblasts (Study KMI00002, GLP)

A study was conducted to evaluate the phototoxicity potential of WST11 as measured by a reduction in neutral red uptake in cultures of Balb/c 3T3 mouse fibroblasts exposed to test article in the presence versus absence of light. The photo-irritancy factor (PIF) was evaluated according to the ZEBET/ECVAM/COLIPA recommendations and values obtained (> 0.795 and 14.306) during the trials predicted that the test article has a phototoxic potential.

Preliminary Study Evaluating Phototoxic Potential at 753 nm after Single Injection by Intravenous Route in the Guinea Pig (Study CERB 20040426TCO, GLP)

A preliminary study examined four different energies (0.73, 2.90, 3.99, and 5.80 J/cm^2) were used to simulate a 20 min skin exposure to the sun. WST11 was administered intravenously at 20 and 50 mg/kg. Guinea pigs treated with WST11 at 20 and 50 mg/kg presented mild to moderate erythema and/or edema at laser energies of 2.90, 3.99, and 5.80 J/cm^2, but not at 0.73 J/cm^2.

Study Evaluating Phototoxic Potential at 753 nm after Single Injection by Intravenous Route in the Guinea Pig (Study CERB 20040427TCO, GLP)

A subsequent study was conducted to evaluate any possible phototoxic potential after single IV injection of 50 mg/kg to guinea pigs. Under the experimental conditions adopted, the animals treated with 50 mg/kg and exposed to the laser energies of 3.99 and 5.80 J/cm^2 presented skin lesions at 24 and 48 hours.

Study Evaluating Phototoxic Potential after Single Injection by the Intravenous Route (Study CERB 20040263STC, GLP)

A further study was conducted to evaluate any possible phototoxic potential of WST11 following single IV injection of 150 mg/kg to guinea pigs (3 Groups of 10 animals (5/sex) exposed to UVA and UVB in the guinea pig. Under the experimental conditions adopted, WST11 (batch 85C91030) formulated at 150 mg/kg (30 mL/kg) was phototoxic in the guinea pig.

2.3.5. Ecotoxicity / environmental risk assessment

Table 8 Summary of main study results

Substance (INN / Invented Name): WST11/ Tookad			
CAS-number (if available): 698393-30-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Unknown	-0.19*	Potential PBT (N)
PBT-assessment			
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (based on 3 and 5 years prevalence)	0.00196 0.00294	µg/L µg/L	> 0.01 threshold (N)
Phase II Physical-chemical properties and fate			
n/a			
Phase IIa Effect studies			

n/a
Note: *determined by *A Brandis et al*.

Padeliporfin di-potassium $PEC_{surfacewater}$ value is below the action limit of 0.01 μg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5.

Therefore, padeliporfin di-potassium is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Results from the submitted pharmacology studies suggest that intraprostatic VTP with padeliporfin dose of 2 mg/kg together with a light dose of 200 J/cm is efficient in inducing necrosis in the dog prostate. In addition, no major secondary effects, changes in heart rate, oximetry, or body temperature have been observed thus far. No evidence of thrombosis in other organs (lung, pulmonary artery, and liver tissues) has been observed, confirming that the VTP effect is localized to the prostate.

The results of studies in other tissues such as biliary, lung and renal tissue did not reveal toxicity on haemodynamic parameters (data not shown).

Given the mechanism of action for padeliporfin, secondary pharmacology studies are not considered necessary.

Safety pharmacology of padeliporfin is considered sufficiently investigated. No effects on CNS, airway function (except a slight bronchodilation at high dose, 150 mg/kg), bleeding time were observed. Padeliporfin had also no effect on behaviour and physiological function. A very low liability for prolonged QT interval was shown in the hERG *in vitro* test and based on this weak signal, two *in vivo* cardiovascular safety pharmacology studies were conducted. In the first cardiovascular safety pharmacology study (Study PLG/MLT 03671N) there were concerns about analytical methods used to quantify plasma sampling and therefore no conclusion can be drawn. However, in the second study the NOAEL was close to 100 mg/kg providing an acceptable margin of safety of at least 14-fold based on comparison of plasma concentration measured at the end of the infusion in monkeys (986 to 1316 g/ml) compared to the Cmax of 70 g/mL in humans at the expected therapeutic dose of 4 mg/kg. In the 2-week repeated-dose toxicity study in cynomolgus monkeys no ECG changes were observed.

The pharmacokinetics programme for padeliporfin was limited but acceptable. Absorption studies were not provided which is accepted considering padeliporfin will be administered via IV route. Data on exposure however has been obtained from the completed toxicology studies in rats and monkeys.

Both rodent and non-rodent, repeat-dose toxicokinetic studies were conducted using padeliporfin administered intravenously over a range of 25 to 150 mg/kg/day. These doses far exceed the anticipated therapeutic range of padeliporfin in humans (2 to 6 mg/kg). There were no apparent toxicokinetic differences observed between sexes, and no evidence of accumulation was seen. Although none of the studies were specifically designed to assess dose linearity, Cmax was found to increase in a linear fashion with the increase of padeliporfin dose in monkeys. This linear relationship was not as evident in the rat, as Cmax does not proportionately increase with the dose level. Dose escalation within this range did not result in increased toxicity.

Based on three *in vitro* biotransformation studies the applicant assumes that padeliporfin is metabolically stable. It is assumed that padeliporfin is poorly distributed and undergoes faecal excretion based on evidence from a small rat distribution study. Considering that treatment with padeliporfin will be a single administration in the indication of prostate cancer, it is unlikely that a significant clinical risk of accumulation of metabolites would occur. Given the results obtained from human dosing it is reasonable to assume that renal excretion of padeliporfin is negligible (see Clinical Pharmacology section). The limited data obtained from Study PKH/MLT 03672N implies distribution to liver and plasma followed by rapid elimination, most likely biliary before faecal elimination.

No investigation of potential drug-drug interactions with padeliporfin was provided based on the assumption that padeliporfin is metabolically stable and rapidly undergoes faecal elimination, which is acceptable. The effect of padeliporfin as a perpetrator of drug interactions is further discussed in the Clinical section.

Single dose toxicity studies in rodents were carried out by IV route at doses up to 400 mg/kg showing essentially CNS and respiratory toxicity for high doses with a large safety margin compared to human clinical dose. No target organs were identified in repeat dose studies in rats, with a NOAEL proposed at the top dose (150 mg/kg). In monkeys, CNS effects, bradycardia, decrease in food consumption, and regenerative anaemia were observed for the high doses and the NOAEL was proposed at 25 mg/kg for the 2 week study because 50 mg/kg was not tested. However, the NOAEL is probably at 50 mg/kg, as proposed in the 7-day study. Liver was not identified as a target organ, a main difference with the predecessor WST09.

In vitro genotoxicity testing identified padeliporfin as having weak potential to induce clastogenicity when illuminated by ultraviolet (UV); this correlates with the mechanism of action (formation of reactive oxygen species) (see SmPC section 5.3).

Padeliporfin was shown to be cytotoxic in the presence of UVA irradiation (*in vitro)* and considered phototoxic in the guinea pig (*in vivo*) (see SmPC section 5.3).

Carcinogenicity, reproductive and developmental toxicity studies have not been conducted with padeliporfin (see SmPC section 5.3). This is considered acceptable given that padeliporfin will be administered acutely, and will be treated to male prostate cancer patients only. All stages of spermatogenesis have been observed in animal. Minimal seminiferous epithelial degeneration was also recorded in one high dose male with vacuolation. All these changes were considered to be incidental and probably related to the intravenous administration procedure (see SmPC section 5.3).

Prostate fluid is a component of the ejaculate. It is not known if the results of Tookad activation in the prostate will affect sperm. To avoid any paternally transmitted damage to the offspring it is recommended as a precautionary measure to avoid pregnancy until any hypothetically damaged cells are removed through spermatogenic cycling. If the patient is sexually active with women who are capable of getting pregnant, he and/or his partner should use an effective form of birth control to prevent getting pregnant during a period of 90 days after the VTP procedure (see SmPC section 4.6).

Regarding blood compatibility, due to the colour of padeliporfin solution, the evaluation of the haemolytic potential of padeliporfin was not possible in rat, monkey, or human blood. The clinical evidence available at the moment is sufficient to rule out an haemolytic cause of concern for padeliporfin.

The submitted ERA was updated with the calculation of the PEC surface water considering the prevalence data from 2012. The PECs surface water, based on both Fpen-values, was well below the action limit of 0.01 µg/L. The obtained PECs values are considered conservative enough considering the proposed indication and hospital administration. The determination of log P for palladium-bacteriopheophorbide can be supported.

Overall, it is agreed that the use of Tookad will not pose a risk to the environment and the wording introduced to the Section 6.6 of SmPC and to PL are considered adequate, i.e. any unused medicinal product or waste material should be disposed of in accordance with local requirements.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical data package is considered acceptable. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity (see SmPC section 5.3).

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.

Table 9 Tabular overview of clinical studies

Study ID	No. of centres / locations	Design	Posology	Objective	Subjects included / planned	Duration	Diagnosis Incl. criteria	Primary Endpoint
HPC/MLT 041228N /MLT 1.01 Phase 1	1 France 24 Jan- 3 July 2005 Completed	Open label, escalating consecutive doses.	Single doses of 1.25, 2.5, 5, 7.5, 10 and 15 mg/kg of WST11 as 10- minute IV injection, Without laser illumination	Evaluate the clinical and laboratory safety and tolerability profiles of WST11 & determine PK parameters of WST11	42/42	3 weeks (2 weeks screening, 2 days hospital, final visit 6 days post dose	Healthy male Caucasian subjects, aged 18 to 40 years, body weight 60 - 80 kg	Evaluate the clinical and laboratory safety and tolerability profiles
CLIN801 PCM201 Phase 2	8 Canada, UK, France, Netherlands Sept 2008/Jan 2011 Completed	Prospective, multicentre, open label, single-dose, escalating study. No control	TOOKAD® 2.0, 4.0 or 6.0 mg/kg; 4 light energies 200 or 300 Joules/cm 10 min IV infusion +22.2 min illumination	Determine optimal drug dose /light energy Safety QoL Effects of 2nd VTP treatment PK	42/40	6-month FU + retreatments	Low risk PCa Eligible for active surveillance Up to T2a Gleason⩽6 PSA<10 mg/ml	Negative biopsies in the treated lobe at Month 6
CLIN901 PCM202 Phase 1/2	5 USA Jul 2009/ Jul 2012 Completed	Prospective, multicentre, open label, single-dose, escalating study. No control	TOOKAD® 2.0, 4.0 or 6.0 mg/kg 200 or 300 Joules/cm 10 min IV infusion +22.2 min illumination	Determine optimal drug /light doses Safety & QoL PK, PD, necrosis at D7 MRI	30/30	6-month FU + retreatments	Unilateral, localized PCa; refused curative therapy. Up to T2A, PSA<10 ng/mL Gleason score ⩽6; ⩽50% of biopsy cores positive; tumour length	Negative biopsies in the treated lobe at Month 6

							⩽5 mm per core	
CLIN902 PCM203 Phase 2	7 France, UK, Netherlands Sept 2009/ Dec 2011 Completed	Prospective, multicentre, open label, single-dose No control	TOOKAD® 4.0 or 6.0 mg/kg 200 or 300 Joules/cm 10 min IV infusion +22.2 min illumination	Confirm optimal drug /light doses Safety & QoL	86/90	6-month FU + retreatments	Up to cT2b PSA<10 ng/mL Gleason score ⩽ 6. 2°pattern 4 acceptable if in < 3 cores from each side & <3mm core length	Negative biopsies in the treated lobe at Month 6
CLIN1001 PCM301 Phase 3	47 Belgium, Finland. France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland, UK Mar 2011/June 2015 Completed	Prospective, multicentre, open label, single-dose, randomized controlled study versus Active Surveillance	TOOKAD® 4.0 mg/kg 200 or 300 Joules/cm; 10 min IV infusion +22.2 min illumination Or Active Surveillance	Efficacy Safety QoL	413/400 (206 TOOKAD 207 active surveillance)	2 years	Gleason⩽ 6 2 to 3 cores positive; if only 1 core ≥3 mm of cancer core length, <5 mm in any core Up to T2a PSA <10 ng/mL Prostate volume ⩾ 25 ⩽ 70 cc	Negative biopsies in the treated lobe at Month 24 Rate of progression to moderate risk or higher
CLIN1201 PCM304 Phase 3	3 Mexico, Panama, Peru May2013/ Dec 2014 Completed	Prospective, multicentre, open label, single-dose No control group	4.0 mg/kg 200 or 300 J/cm 10 min IV infusion +22.2 min illumination	Efficacy Safety QoL	81/80	24 months	Localized PCa; Gleason 6 Gleason 3+4 acceptable if in ⩽ 2 cores and <50% cancer in any core Clinical stage ⩽cT2a Prostate volume ⩾ 25 & ⩽ 70 cc. PSA < 20 ng/mL.	Negative biopsies in the treated lobe at Month 24
Long term follow up:								
CLIN801 PCM 201 and CLIN902 PCM 203 Phase 2	7 France, UK, Netherlands 2011 / 2016 On-going	Long term follow up (LTFU) No control group		LTFU safety and efficacy of patients from two phase II clinical trials	122/125	5 years	Low risk PCa, eligible for active surveillance Up to T2a Gleason ⩽6 PSA<10 mg/ml	Adverse events Biopsy results Radical treatments
PCM301 FU5 Phase 3	On-going	Open, observ-ational extended follow-up	No intervention is mandated	LTFU safety and efficacy	Up to 413	Additional 60 months, total 84 months (7 years)	All subjects originally randomized in study CLIN1001 PCM301	

2.4.2. Pharmacokinetics

The pharmacokinetic properties of Tookad were studied in 42 healthy human male subjects (without photoactivation) (Study MLT-1.01) and in 70 patients with localised prostate cancer (after photoactivation) (Study CLIN801PCM201 and Study CLIN901PCM202).

In **Study MLT-1.01**, the PK parameters of WST11 were evaluated in 42 healthy male subjects, aged between 18 and 40 years with a BMI of 19 to 29.0 kg/m^2. The study was conducted between 24 January and 3 July 2005. WST11 was administered as a single, 10 min, intravenous infusion at escalating doses of 1.25 to 15 mg/kg and the catheter was removed immediately after the end of the injection.

In **Study PCM201**, the PK parameters of Tookad were evaluated in 40 male patients suffering from localized prostate cancer. Tookad was administered as a single, 10 min, intravenous infusion at escalating doses of 2, 4 and 6 mg/kg followed by percutaneous transperineal interstitial irradiation with laser light at 753 nm at 200 J/cm, using fibres positioned in the prostate lobes.

In **Study PCM202**, PK of Tookad was evaluated in 30 patients suffering from localized prostate cancer. Tookad was administered as a single, 10 min, intravenous infusion at escalating doses of 2 and 4 mg/kg. This was followed by light activation delivered through one or multiple transperineal interstitial optical fibres using 753 nm laser light at escalating fixed energy doses of 200 J/cm and 300 J/cm.

Standard plasma PK parameters were calculated: Cmax (ng/mL), Tmax (h), AUCt (ng/mL.h), AUCinf (ng/mL.hr) and %AUC extra (percentage of extrapolated AUC), plasma half-life, plasma clearance and apparent volume of distribution.

Absorption

Tookad is administered intravenously and is therefore completely bioavailable.

Distribution

In healthy human male subjects, the mean volume of distribution ranged from 0.064-0.279 L/kg, for posologies from 1.25 to 15 mg/kg of padeliporfin di-potassium indicating distribution into extracellular fluid. A similar mean distribution volume was seen in patients with localised prostate cancer treated with 2 and 4 mg/kg of padeliporfin di-potassium (0.09-0.10 L/kg respectively).

Study PKH/MLT04691N investigated two *in vitro* methodologies, equilibrium dialysis and partitioning, to determine the binding of WST11 to plasma proteins. Results showed that blood partitioning allowed for the characterization of a binding process between WST11 and plasma proteins with a value of binding percentage of 98.97%.

The distribution of WST11 *in vitro* between human blood cells (mostly erythrocytes) and plasma was also investigated. No binding to red blood cells occurred in the presence of plasma protein, indicating that WST11 has a higher affinity for plasma protein than for blood cells.

Elimination

Clearance of padeliporfin di-potassium in healthy male subjects treated from 1.25 mg/kg up to 15 mg/kg of padeliporfin di-potassium ranged from 0.0245 to 0.088 L/h/kg. Based on popPK analysis (see further below) the estimated half-life is 1.19 h ± 0.08 at 4 mg/kg of padeliporfin di-potassium. A similar mean clearance range was seen in patients with localised prostate cancer treated with 4 mg/kg and 2 mg/kg of padeliporfin di-potassium (0.04-0.06 L/h/kg respectively). Urinary excretion of padeliporfin in healthy human subjects was very low (< 0.2 % of the dose).

No specific studies to study excretion in humans were provided. Taking into account its molecular mass and the very low urinary excretion of the molecule, faecal elimination is the most probable route of elimination in human.

Dose proportionality

The pharmacokinetic population in study MLT-1.01 included all the subjects who received one dose of the study drug and for whom a complete pharmacokinetic profile was available (N=41). The results from study MLT-1.01 obtained for plasma analysis showed that Cmax increased linearly with the doses from 1.25 to 15 mg/kg of WST11 covering the therapeutic range. Tmax was unchanged whatever the dose between 1.25 and 15 mg/kg of WST11. The terminal plasma half-life (t1/2) at 15 mg/kg was 8 h ± 4 h. Due to low plasmatic concentration on lower doses, t1/2 could only be determined at the highest dose and no comparison among other doses is given. The AUCt increased linearly with the doses from 1.25 to 10 mg/kg.

In Study CLIN801 PCM201, the pharmacokinetic parameters of Tookad were evaluated in 40 male patients suffering from localized prostate cancer. Five patients were re-treated (dose 4 mg/kg).

Table 10 Pharmacokinetics parameters following a WST11 10 minutes intravenous infusion (first administration and after retreatment), Study CLIN801 PCM201

Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)*	AUC_t (ng/mL*h)	AUC_{inf} (ng/mL*h)	%AUCextra	K_{el} (1/h)	$t_{1/2}$ (h)	Cl (L/h/kg)
2	21830.68 ± 4760.69	0.21	65091 ± 38851	74854	0.43	0.61	1.14	0.03
4	70449.54 ± 13862.41	0.15	175555 ± 50488	178037 ± 51582	0.64 ± 1.06	0.60 ± 0.13	1.24 ± 0.45	0.02 ± 0.01
6	82740.99	0.13	321596	322966	0.54	0.63	1.16	0.02

* Median

** When calculable (n ≥ 3)

Pharmacokinetics parameters in patients after retreatment (n=5)

Dose (mg/kg)	Subject	Cmax (ng/mL)	Tmax (h)	AUCt (ng/mL*h)	AUCinf (ng/mL*h)	%AUCextra	Kel (1/h)	$t_{1/2}$ (h)	Cl (L/h/kg)	Vd (L/kg)
4	n	5	5	5	5	5	5	5	5	5
	Mean	69365.58	0.17	151976	152466	0.36	0.58	1.21	0.03	0.05
	Stdev	23983.63	0.00	50041	50078	0.18	0.08	0.18	0.01	0.03
	%CV	34.58	0.00	32.93	32.85	49.72	14.23	14.86	46.58	52.47
	GeoMean	65300.63	0.17	143720	144238	0.33	0.58	1.20	0.03	0.05
	Median	73019.25	0.17	168033	168451	0.26	0.58	1.19	0.02	0.04
	Min	32775.44	0.17	73962	74456	0.25	0.47	1.03	0.02	0.03
	Max	99082.44	0.17	205378	205908	0.66	0.67	1.47	0.05	0.10

In the study CLIN901 PCM202, the pharmacokinetic was evaluated on 30 patients suffering from localized prostate cancer. The first three patients entered into the study were treated with WST11 2 mg/kg with 200 J/cm, and the next six patients have been treated with WST11 2 mg/kg with 300J/cm. The remaining 21 patients were treated with WST11 4 mg/kg with 200 J/cm.

Table 11 Pharmacokinetics parameters following a WST11 10 minutes intravenous infusion (first administration and after retreatment), Study CLIN901 PCM202

Pharmacokinetic parameters following a WST11 10 minutes intravenous infusion

Dose (mg/kg)	Subject	Cmax (ng/mL)	Tmax (h)	AUC_t (ng/mL*h)	AUC_{inf} (ng/mL*h)	%AUCextra	$t_{1/2}$ (h)	Cl (L/h)	Vd (L)	Ae_t (ng)	Ae_{inf} (ng)	CLr (mL/h)	fe%
2	N	9	9	9	9	9	9	9	9	8	8	8	8
	Mean	30883.83	0.43	41435	43923	4.70	1.25	4.05	6.50	158617	167293	5.14	0.12
	Stdev	11583.07	0.61	21410	24295	4.78	0.90	2.02	5.18	96803	108938	6.84	0.08
4	N	20	20	20	19	19	19	19	19	15	15	15	15
	Mean	57102.87	0.25	106016	108121	5.42	1.69	3.17	6.69	785319	880286	7.13	0.31
	Stdev	14849.50	0.22	55575	48824	18.41	1.11	1.56	3.43	1720496	1738485	14.14	0.62

Pharmacokinetic parameters following a WST11 10 minutes intravenous infusion for patients after retreatment

Dose (mg/kg)	Subject	Cmax (ng/mL)	Tmax (h)	AUCt (ng/mL*h)	AUCinf (ng/mL*h)	%AUCextra	$t_{1/2}$ (h)	Cl (L/h)	Vd (L)	Aet (ng)	Aeinf (ng)	CLr (mL/h)	fe%
4	N	5	5	5	5	5	5	5	5	4	4	4	4
	Mean	63128.68	0.40	147147	152808	7.37	0.88	3.02	3.06	568915	609178	2.80	0.22
	Stdev	26517.90	0.37	88771	87236	9.55	0.25	3.01	1.65	734000	801404	3.05	0.29

Population PK analysis

Based on data from study MLT-1.01, WST11 concentration time data were modelled with two-compartment model with a zero-order bolus dose, an infusion whose duration is modelled. A strong effect of the dose on clearance was included using the Emax model. Between-subjects (IIV) variability on PK parameters: clearance (CL), volume of distribution of central compartment (V), inter-compartmental clearance (Q), volume of distribution of peripheral compartment and duration of infusion was estimated with exponential variance models and a proportional variance model described the residual error. A first order conditional estimation (FOCE) method with interaction was used. The effect of demographic factors on apparent clearance was initially assessed graphically. No obvious effect of any demographic factors could be observed on the plots of between subjects' variability (individual deviations from the population value) on clearance versus demographic co variates (weight, height, BSA, BMI and age). These effects were further evaluated by univariate analysis. No demographic factor affected the PK parameters of WST11. The apparent clearance decreased with increasing actual dose following an Emax model. The population apparent clearance ranged from 6 L/h (dose of 79 mg) to 1.98 L/h (dose of 1110mg). The duration of infusion was estimated at 0.204 h (or 12 minutes). The volume of distribution of central compartment was 3 L, and the volume of the peripheral compartment was 1.15 L.

The inter-compartmental clearance was 0.137 L/h. Between subjects' variability on clearance and volumes was low. The between subjects' variability of inter compartment clearance was greater, around 50 %. The variability on the duration of infusion was low, 12%. The residual variability was low to moderate with a CV of 21%.

Based on the estimation of the Inter-occasion variability on 10 patients that were re-treated, intra-individual variability was found to be low for infusion duration (25.4%), clearance (20.2%) and volume of the central compartment (23.9%). Intra-individual variability was high for inter-compartmental clearance (56.7%) and for volume of the peripheral compartment (81.4%).

The applicant provided the conclusions obtained in several subsequent evaluations of the PopPK model that was initially developed (data not shown). Several re-runs of the initial model were done with different subsets of the available data. To further substantiate the similarity of PK between healthy subjects and patients, the original model was run independently with two subsets of data (heathy or patients), resulting in model parameters that were, generally, similar. To further substantiate the effect of the continuous illumination of the targeted prostate area, a statistical comparison (Wald test) was performed to gauge the effect of the laser exposure intensity on each PK parameter. Only the perfusion time (D) and inter-compartmental clearance were shown to be different between treatments, which can be explained by a different collection protocol. Similar approaches on the race, age, ALB, ProTime, BIL, ALAT, ASAT, GGT and ALCPH as covariates, had shown no relevant findings with implications on the PK of WST11.

Special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	23/118 (19.5 %)	3/118 (2.5 %)	1/118 (0.8 %)

Pharmacokinetic interaction studies

Tookad (WST11) was investigated in *in vitro* studies as an inhibitor of cytochrome P450 (CYP450) enzymes in human liver microsomes and as an inhibitor of transporters in human recombinant CHO cells (see table below). The following table details the estimation of human exposure from clinical data.

Table 12 Human exposure data for WST11

Parameter	**Result**
Human dose	4 mg/kg
MW salt (base)	916.4 (838.2)
Human C_{max} (mean)	70,449.54/57,102.87 ng/mL 8.40E-05/6.81E-05 M
Human fu	0.01
Human free C_{max}	8.40E-07/6.81E-07 M

Table 13 *In vitro* inhibition parameters determined for WST11

Inhibition parameter	IC_{50} (M)
BSEP	6.17E-06
OCT2	> 1.0E-04
BCRP	N.C.
OAT1	N.C.
OAT3	N.C.
OATP1B1	2.9E-07
OCT1	> 1.0E-04
OATP1B3	2.4E-07
P-gp	N.C.

N.C.: Not calculable, inhibition was not observed across the range of concentration tested (3.0E-8 to 1.0E-04 M)

The ratio of free C_{max} concentrations of WST11 observed in clinical studies PCM201 and PCM202 to the IC_{50} values for each transporter and CYP450 enzyme tested are listed in the below table.

Table 14 Interaction risk assessment at human dose of 4 mg/kg

Enzymes/Transporters	WST11 ratio (based on mean free C_{max} from PCM201)	WST11 ratio (based on mean free C_{max} from PCM202)	Interaction potential
BSEP	0.14	0.11	Possible Interaction risk
OCT2	N.A.	N.A.	No Interaction
BCRP	N.A.	N.A.	No Interaction
OAT1	N.A.	N.A.	No Interaction
OAT3	N.A.	N.A.	No Interaction
OATP1B1	2.90	2.35	Possible Interaction risk
OCT1	N.A.	N.A.	No Interaction
OATP1B3	3.50	2.84	Possible Interaction risk
P-gp	N.A.	N.A.	No Interaction

N.A. Not applicable.

Note: Interaction potential is identified as a possible interaction risk when the ratio between human free C_{max} and in vitro IC_{50} < 0.02.

Additional tests were conducted to study the *in vitro* CYP inhibition in optimal conditions (protection from light) (see table below). Direct inhibition was tested in various CYP isoforms.

Table 15 *In vitro* CYP inhibition (direct) parameters were determined for WS11 in controlled conditions – cyprotex results

CYPs	Experimental conditions	IC50 (µM)	Data source
CYP1A2	WST11 DS in DMSO (protected from light)	>5	Cyprotex study CYP1482 R2
	WST11 DS in degassed distilled water (protected from light)	31.6	Cyprotex study CYP1482 R5
CYP2B6	WST11 DS in DMSO (protected from light)	>5	Cyprotex study CYP1482 R2
	WST11 DS in degassed distilled water (protected from light)	37.2	Cyprotex study CYP1482 R5
CYP2C8	WST11 DS in DMSO (protected from light)	>5	Cyprotex study CYP1482 R2
	WST11 DS in degassed distilled water (protected from light)	>50	Cyprotex study CYP1482 R5
CYP2C9	WST11 DS in DMSO (protected from light)	>5	Cyprotex study CYP1482 R2
	WST11 DS in degassed distilled water (protected from light)	>50	Cyprotex study CYP1482 R5
CYP2C19	WST11 DS in DMSO (protected from light)	>5	Cyprotex study CYP1482 R2
	WST11 DS in degassed distilled water (protected from light)	>50	Cyprotex study CYP1482 R5
CYP2D6	WST11 DS in DMSO (protected from light)	>10	Cyprotex study CYP1482 R2
	WST11 DS in degassed distilled water (protected from light)	>50	Cyprotex study CYP1482 R5
CYP3A (midazolam substrate)	WST11 DS in DMSO (protected from light)	>5	Cyprotex study CYP1482 R2
	WST11 DS in degassed distilled water (protected from light)	35.5	Cyprotex study CYP1482 R5
CYP3A4 (testosterone substrate)	WST11 DS in DMSO (protected from light)	>5	Cyprotex study CYP1482 R2
	WST11 DS in degassed distilled water (protected from light)	>50	Cyprotex study CYP1482 R5

DS: Drug Substance

Table 16 *In vitro* CYP inhibition parameteres were determined for WST11 in controlled conditions without preincubation and with 30 minutes preincubation with or without NADPH – Cyprotex results

CYPs	Experimental conditions	IC50 (µM) (Pre-incubation)	Fold shift	Data source
CYP1A2	WST11 DS in DMSO (protected from light)	>5 (0 min) >5 (30 min - NADPH) >5 (30 min + NADPH)	ND	Cyprotex study CYP1482 R2 TDI experiment
CYP2B6	WST11 DS in DMSO (protected from light)	>5 (0 min) >5 (30 min - NADPH) >5 (30 min + NADPH)	ND	Cyprotex study CYP1482 R2 TDI experiment
CYP2C8	WST11 DS in DMSO (protected from light)	>5 (0 min) >5 (30 min - NADPH) >5 (30 min + NADPH)	ND	Cyprotex study CYP1482 R2 TDI experiment
CYP2C9	WST11 DS in DMSO (protected from light)	>5 (0 min) >5 (30 min - NADPH) >5 (30 min + NADPH)	ND	Cyprotex study CYP1482 R2 TDI experiment
CYP2C19	WST11 DS in DMSO (protected from light)	>5 (0 min) >5 (30 min - NADPH) >5 (30 min + NADPH)	ND	Cyprotex study CYP1482 R2 TDI experiment
CYP2D6	WST11 DS in DMSO (protected from light)	>10 (0 min) >10 (30 min - NADPH) >10 (30 min + NADPH)	ND	Cyprotex study CYP1482 R2 TDI experiment
CYP3A4 (midazolam substrate)	WST11 DS in DMSO (protected from light)	>5 (0 min) >5 (30 min - NADPH) >5 (30 min + NADPH)	ND	Cyprotex study CYP1482 R2 TDI experiment
CYP3A4 (midazolam substrate)	WST11 DS in degassed distilled water (protected from light)	>50 (0 min) 12.3 (30 min - NADPH) 17.2 (30 min + NADPH)	0.714*	Cyprotex study CYP1482 R5 TDI experiment
CYP3A4 (testosterone substrate)	WST11 DS in DMSO (protected from light)	>5 (0 min) >5 (30 min - NADPH) >5 (30 min + NADPH)	ND	Cyprotex study CYP1482 R2 TDI experiment

DS: Drug substance dissolved in DMSO; ND: Not Determined (the fold shift in IC50 could not be determined for any isoform due to the lack of measurable IC50 values).

* WST11 inhibition of CYP3A4 did increase with incubation time but this was not dependent on P450 activity, indicating that it is not a mechanism based inhibitor of CYP3A4.

The fold shift in IC50 could not be determined for any isoform due to the lack of measurable IC50 values under any of the assay conditions. There was no marked difference in the percentage inhibition achieved following a pre-incubation in the presence or absence of NADPH for any of the isoforms tested. Inhibition following a 30 min pre-incubation with or without NADPH tended to be greater than that observed in the absence of pre-incubation.

In vitro studies were also performed in HEK293 cells to determine if WST11 was a substrate of OATP1B1 or OATP1B3. These studies showed that showed that WST11 is unlikely to be a substrate of OATP1B1 or OATP1B3. Additional *in vitro* experiments were conducted in order to determine the possible uptake and efflux transporters. WST11 was shown not to be a substrate of BSEP, MRP2, OATP2B1 and OCT1 (SLC transporters) (data not shown).

2.4.3. Pharmacodynamics

Mechanism of action

No study submitted.

Primary and Secondary pharmacology

Prostate necrosis on Day 7 gadolinium multi-parametric Magnetic Resonance Imaging (mp-MRI) scans

The Phase 2 studies (PCM201, PCM202 and PCM203) investigated, in an exploratory fashion, the relationship between energy delivery and prostate necrosis (see also section on dose-response studies). An adjusted prostate volume was used to account for transient prostate swelling. Prostate volume was enlarged at Day 7 post treatment before decreasing by Month 3 and again slightly at Month 6. The adjusted Day 7 prostate necrosis percentage was the proportion of prostate necrosis volume in the treated lobe by planimetry compared with half the prostate volume by planimetry considering the average between the baseline and Day 7 volumes. The prostatic necrosis % conveys the proportion of necrosis in the treated lobe without reference to the tumour.

Study CLIN801 PCM201

Study Title: Vascular-Targeted Photodynamic therapy using WST11 in patients with localized prostate cancer.

This study was conducted in England, France and Canada, with a total of 8 sites that recruited subjects.

Forty subjects received a single IV administration dose of WST11 (2, 4 or 6 mg/kg and 10-minute infusion) followed by continuous illumination of the prostate gland through optical fibres at 753 nm (200J/cm), for 22 minutes and 15 seconds, starting after the end of the infusion.

Primary objective: to identify optimal treatment conditions. Apart from the dose of the drug, other parameters are the total energy delivered and the density of energy delivered by unity of prostate volume.

The total energy delivered was calculated by multiplying the laser-applied energy (200J/cm) by the total length in centimetres of the illumination tip of the fibres (all fibres used are considered). The figure below shows the correlation between the total energy delivered (in Joules) and volume of necrosis observed at day 7 (in cm^3).

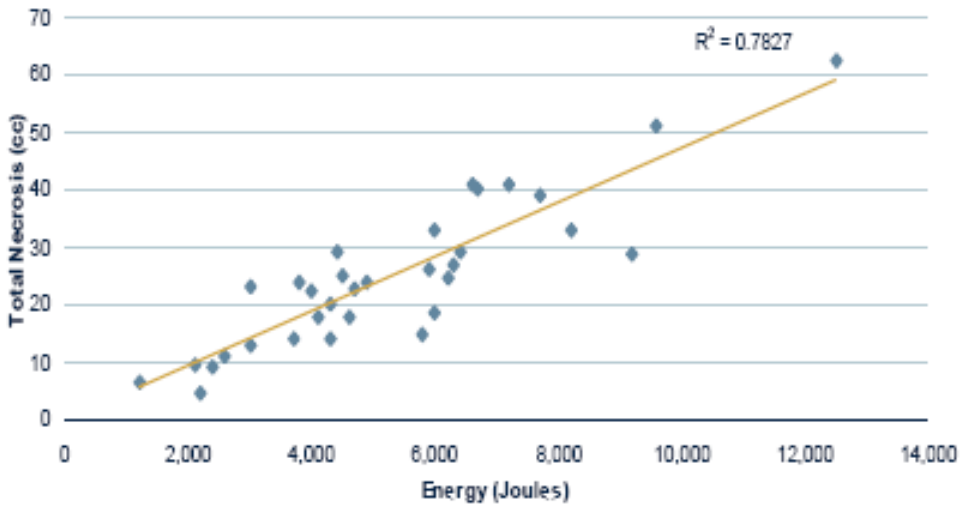


Figure 2 Correlation between the total energy delivered and volume of necrosis observed at day 7 (33 subjects treated at 4 mg/kg and 200 J/cm)

The mean necrosis volume at Day 7 after treatment, of all doses combined (38 patients) was fairly low at 24.2 mL (37.8%). Prostate necrosis % was higher with 4mg/kg Tookad [42.2% ± 18.2 (range 11.5-80.0%)] compared to 2mg/kg (7.2%) and 6mg/kg (12.2%). Bilateral treatment mean necrosis volume at Day 7 was 36.7 mL (51.9%) for 14 patients compared to 19.8 mL (35.0%) for 19 patients receiving unilateral treatment with 4mg/kg WST11.

To take into account the density of energy used by unit of prostate volume, a 'Light Density Index' (LDI) corresponding to the ratio of cumulated lengths (in centimetres) of illumination tip of the fibres used, to the volume of prostate intended to be treated (in cubic centimetres) was calculated (i.e. LDI = N cm of illumination tip of the fibres at 200 J/cm/N cm^3/ targeted prostate volume). A target threshold of 1 was defined (Light Density Index <1 or ≥1). This was identified on the basis of the percentage of necrosis at Day 7.

The table below shows that the mean percentage of necrosis of the targeted prostate tissue in patients treated with a therapeutic Light Density Index ≥1 was significantly higher than for patients with an index <1: 95% versus 59% (p<0.01).

Table 17 Percentage necrosis according to the LDI applied in PCM201 study

Light Density Index	N*	Mean % Necrosis / Mean Prostate/lobe volume	p value
< 1	17	59.0%	< 0.01
≥ 1	12	95.0%	

* Patients with MRI data available at day 7, treated with 4 mg/kg of TOOKAD®, with 3 fibres or more and analysable (i.e. no major violation of protocol).

Biopsy Results

38 subjects were included in the efficacy (evaluable) population, out of which 28 subjects were included in the optimal dose-energy population (4 mg/kg and 200 J/cm).

Of the 38 subjects, 8 had a bilateral disease and were treated bilaterally, 7 had a unilateral disease but treated bilaterally, and the remaining 23 subjects were treated unilaterally.

For all types of treatment in the efficacy population, 20 of 38 subjects (52.6%) had a negative biopsy, 17 (44.7%) had a positive biopsy and 1 (2.6%) had no biopsy performed at month 6.

Of the 28 patients treated per protocol with 4 mg/kg (whatever the LDI applied), 15 (53.6%) had negative biopsies at 6 months and 13 (46.4%) had positive one. The one-sided exact binomial probability of this observation (compared to the 40%/60% rate expected) was 0.10 (power 90%), that is just above the preset level of significance (<0.10).

When only the 12 patients treated under optimal treatment conditions (dose of 4 mg/kg and LDI≥1) were considered, the percentage of negative biopsies was 83.3%, which was associated with an exact probability of 0.003 as compared to expectations (this was considered as an exploratory analysis). The table below summarizes these results.

Table 18 Biopsy results in PCM201 study (4 mg/kg – 200 J/cm)

	No. patients treated	No. of patients with Positive or unavailable biopsies (%)	No. of patients with Negative biopsies (%)	p (compared to 0.40)
All ITT 4 mg/kg patients	34	17 (50%) (16 positive, 1 unavailable)	17(50%)	0.16
Per Protocol treated with 4 mg/kg	28	13 (46.4%)	15 (53.6%)	0.10
Per Protocol -with LDI≥ 1 (exploratory)	12	2 (16.7%)	10 (83.3%)	0.003

LDI= Light Density Index

The study also showed that simultaneous bilateral treatment was less likely to allow complete coverage with an adequate LDI in both lobes.

Study CLIN801 PCM202

Study Title: “A Prospective, multicenter phase 1/2 safety and tolerability study of unilateral Vascular-Targeted Photodynamic Therapy using WST11 in patients with localized Prostate Cancer

This study was conducted in the United States of America, with a total of 5 sites that recruited subjects.

Primary objective: to define the study drug and light dosage combination that achieves negative biopsy in the treated lobe at Month 6 and to determine the local safety and tolerability effects, including toxicity, of Tookad VTP treatment in patients with localized prostate cancer.

This was an exploratory study with the main objective to determine optimal treatment conditions. It was started before these optimal treatment conditions were determined from PCM201 and PCM203.

As data from those studies became available, a decision was made to treat the remaining patients with 4 mg/kg, 200 J/cm.

Table 19 Number of patients per treatment scheme in the PCM202 study

	2 mg/kg single fibre	2 mg/kg multiple fibres	4 mg/kg multiple fibres	Total
200 J/cm	0	3	21	24
300 J/cm	3	3	-	6
Total	3	6	21	30

Day 7 necrosis percentage was greater in the higher treatment group (64.1% with 4 mg/kg WST11, 200 J/cm Light Energy Level) and this was variable between individuals (4.8-108.9%), partly due to differences in prostate size. In comparison % prostatic necrosis was 46.9% with 2mg/kg WST11, 200J/cm. Prostate necrosis % was lower with 300J/cm (13.8%) than 200J/cm combined with 2mg/kg Tookad, possibly because only a single fibre was used.

Overall, 19 patients out of 30 (63.3%) had negative biopsies in the treated lobe at Month 6. In patients treated with optimal dose and light optimal conditions and a LDI ≥ 1, the percentage of negative biopsies was 73.3%.

Table 20 Negative biopsies at 6 months in PCM202

	2 mg/kg 200 J/cm	2 mg/kg 300 J/cm	4 mg/kg 200 J/cm			Total
			LDI < 1	LDI ≥ 1	ALL LDI	
Total	3	6	6	15	21	30
Negative	3	3	2	11	13	19
% negative biopsies	100.0 %	50.0 %	33.3 %	73.3%	61.9 %	63.3 %

Study CLIN801 PCM203

Study Title: "Vascular-Targeted Photodynamic Therapy using WST11 in patients with localised prostate cancer".

This was a European multi-centre, Phase 2, open label trial.

Primary objective: to determine the optimal treatment conditions (study drug dose, light dose, number of fibres, length of fibres, and configuration of fibres) to achieve prostate cancer tumour ablation and to assess the effects of Tookad VTP treatment in patients with localized prostate cancer).

A total of 86 patients have been included in this study, one patient did not receive the study drug; the remaining 85 patients have been treated according to the following groups:

- Group TS1 corresponded to conservative hemiablation with 4 mg/kg, 200 J/cm and a high density of fibre-energy applied (close to optimal treatment conditions that were defined in PCM201).

- Group TS2 was conservative suboptimal ablation of the whole gland, with 4 mg/kg and 200 J/cm and a safe use of a high density of fibre (suboptimal density).
- Group TS3 corresponded to conservative hemiablation with 6 mg/kg.
- Group TS4 corresponded to treatment with 4 mg/kg, 200 J/cm in one lobe and 300 J/cm in the other lobe.

Prostate necrosis % appeared higher with 4mg/kg Tookad and 200J/cm Light energy in Study PCM203 (87.6% unilateral, 71.5% bilateral) than PCM202. The 6mg/kg Tookad resulted in a lower % necrosis (63.9%) than 4mg/kg Tookad probably due to the lower relative length of the optical fibres to treatment size as discussed later. Again % necrosis was lowest with use of a 300J/cm single fibre (47.7%).

Among the performed biopsies of 83 patients overall 73.5% were found negative for cancer in the treated lobe.

Table 21 Negative biopsies at 6 months in PCM203

Biopsies @ 6 months	TS 1 4 mg/kg 200 J/cm 1 lobe	TS 2 4 mg/kg 200 J/cm 2 lobes	TS 3 6 mg/kg 200 J/cm 1 lobe	TS 4 4 mg/kg 200 and exploratory 300 J/cm of 1 or 3 fibres	Total
Dropped or refused	1	1	0	0	2
Total	46	13	21	3	83
Negative	38	9	13	1	61
% negative Among performed biopsies	82.6	69.2	61.9	33.3	73.5

In patients treated under optimal treatment conditions (Group TS1), the percentage of negative biopsies for cancer in the treated lobe was 82.6%.

Overall conclusion

Extraprostatic necrosis was seen with all dose/ light energy combinations. It tended to increase as intra-prostatic necrosis increased but was proportionally greater with bilateral treatment.

The total energy delivered was calculated by multiplying the laser-applied energy (e.g. 200J/cm) by the total length in centimetres of the illumination tip of the fibres. All 3 studies showed a correlation between the total energy delivered (J) and volume of necrosis observed at Day 7 (cm^3). This was most evident in Study PCM201 in 33 subjects treated with 4mg/kg and 200J/cm (R2= 0.7827) and weakest in PCM203 looking at 4mg/kg and 6mg/kg WST11 (R2= 0.318).

To account for prostate volume as a probable confounding factor the Light Density Index (LDI) was calculated. The LDI corresponds to the ratio of the cumulative length of illuminated fibre tips (cm) to the volume (cc) of the targeted zone to be treated. The targeted zone corresponds to the lobe containing the positive biopsies. Its volume is measured after prostate delineation using the treatment guidance software. The relationship between the LDI and prostate necrosis at Day 7 was investigated in a post-hoc exploratory analysis. In Phase II studies, treatment conditions corresponding to an LDI ≥ 1 were associated with a mean rate of necrosis of the targeted zone at day 7 of 89 % ± 20.75 for unilateral and 79 % for bilateral treatments. These treatments were performed with at least a 3 month interval.

In study PCM203 the linear association between prostate necrosis at Day 7 and the LDI (rather than energy delivered) was stronger, with a Pearson's correlation coefficient of 0.749 ($p<0.0001$). The mean Day 7 necrosis percentage for the patients with LDI ≥1 treated with 4 mg/kg WST11 and 200 J/cm Light Energy Level was 74.3%. There was no relationship between LDI and mean prostate necrosis at Months 3 or 6, which was relatively low across the treatment groups.

Data from study PCM201 was studied in order to establish any concentration-effect relationship between plasma Cmax, length of light-emitting fibres and volume of necrosis. This model gave a correlation between Cmax and volume of necrosis normalised per cm of fibre ($R^2= 0.894$), explaining part of the relation between PK and PD response. LDI allowed data to be normalized with respect to the prostate volume and to study its influence on the volume of necrosis normalised per cm of fibres. The change in R2 (0.894 to 0.896) was minimal by adding the LDI parameter, suggesting no significant influence of the LDI parameter on the volume of necrosis normalised per cm of fibres ($p=0.3759$). Cmax of Tookad is an important influence on the volume of necrosis.

The optimal treatment parameters as determined by these trials were a dose of 4 mg/kg dose of Tookad, a light energy of 200 J/cm and a minimum of 1 for the LDI.

Histopathology

Twelve patients underwent prostatectomy within the 24-month time frame of the Phase 3 study. Pathology reports were obtained for 9 of the 12 patients who underwent radical prostatectomy after Month 12 in the VTP arm in PCM301. The collection of histology data was not planned in the protocol and CRF so it was not possible to get complete information for all the patients. In all except one of the patients there was bilateral tumour; one patient had Gleason 4+3, 6 patients had Gleason 3+4 and 2 patients had Gleason 3+3.

Location of tumour in relation to the area of VTP-induced necrosis was provided in 6 patients. In 5 patients tumour was located outside the VTP scar at a variable distance from 1mm up to fibrosis not visible on the same specimen piece. In one patient tumour was inside the treated area.

Skin phototoxicity

Skin photo- tests were conducted on all subjects in the Phase 1 study MLT1.01. Photosensitization increased with the administered dose of WST11. After irradiation with total solar spectrum and with 1 MED, photosensitization was limited to the first 3 hours after dosing in the 1.25 and 2.5 mg/kg dose groups, to the first 6 hours after dosing in the 5 and 7.5 mg/kg dose groups and to the 24 and 48 first hours after dosing in the 10 and 15 mg/kg dose groups, respectively. One subject in the highest drug dose group (15 mg/kg) had a positive 24-hour photo-test.

Ophthalmic evaluation was performed in the Phase 1 study at screening, after 48 hours and at Day 6; no abnormalities were observed. An inclusion criterion was a normal ophthalmologic exam and subjects were kept in dimmed indoor light for 2 days.

2.4.4. Discussion on clinical pharmacology

Tookad is administered as a single 10-minute intravenous administration of 4 mg/kg. As such, the absolute bioavailability was considered as 100%. Then the prostate is illuminated immediately for 22 minutes 15 seconds by laser light at 753 nm delivered via interstitial optical fibres from a laser device at a power of 150 mW/cm of fibre, delivering an energy of 200 J/cm.

Padeliporfin di-potassium is highly bound to human plasma proteins (99 %). The volume of distribution obtained in the various human studies was around 4 – 6 L. Minimal metabolism of padeliporfin was observed in *in vitro* metabolism studies in human liver microsomes and S9 fractions. No metabolites of padeliporfin were observed in these studies (see non clinical section and SmPC section 5.2). No *in vitro* or *in vivo* studies have been conducted with radiolabelled padeliporfin. Therefore, the possibility for some *in vivo* metabolism of padeliporfin cannot be fully excluded (see SmPC section 5.2).

The comparison of the PK results from the phase 1 study Study MLT-1.01 and the two studies in patients (Study PCM201 and PCM202) showed that there is no significant difference in the kinetics of the drug between patients with prostate cancer and healthy subjects.

Although the continuous illumination duration is small (22 minutes 15 seconds), no assessment was made regarding the eventual effect of this on the overall elimination of the drug. However, this effect is not expected to be significant based on PK parameters obtained in the various clinical studies.

The effects of age, weight and race were investigated in healthy volunteers and patients. The results of the population PK study showed that age, race, and markers of hepatic function were unlikely to have a substantial and biologically significant impact on the pharmacokinetics of Tookad. The body weight of patients (range 60-120 kg) presented a minor impact on the Tookad**.** Tookad pharmacokinetic parameters for doses up to 5 mg/kg of padeliporfin di potassium (see SmPC section 5.2).

No study was conducted in patients with impaired renal function. Very small amount of Tookad soluble is excreted via the kidney. It is not expected that patients with renal impairment would have any alteration in blood levels or excretion. Hence no adjustment in dose is required in these patients.

This medicinal product contains potassium and in general the dose (3.66 mg/kg) will be less than 1 mmol (39 mg) i.e. essentially ‘potassium free’. However, this will be exceeded in patients heavier than 115 kg. This should be taken into consideration in patients with reduced kidney function or patients on a controlled potassium diet where a rise in serum potassium would be considered detrimental (see SmPC sections 4.2 and 4.4).

There is no data available in patients with hepatic impairment. Biliary excretion is the major route of elimination of the drug. Therefore, exposure to padeliporfin is expected to be increased and/or prolonged in patients with hepatic impairment. No specific dosage recommendation can be given. Tookad should be used with caution in patients with severe hepatic impairment (see Section 4.2 of the SmPC). The liver is not a target organ for toxicity and, with a single dose only to be given to cover the VTP procedure, the only increased precautions are the possible need for prolonged protection from light after the patient is discharged assuming that the patient were otherwise considered suitable for general anaesthesia. Therefore, performing a study in subjects with moderate to severe liver impairment, who are unlikely to be candidates for VTP, would not be justified. Tookad is contraindicated in patients who have been diagnosed with cholestasis (see section 4.3).

The majority of patients in the studies performed was 50-year of age or older. There is no relevant use of Tookad in the paediatric population in the treatment of low-risk localised prostate cancer. Very few patients aged over 75 years were enrolled into studies where pharmacokinetic measurements were taken so it is not known if there is a difference in these older patients compared to patients less than 75 years of age. No specific posology adjustment is necessary in this population (see SmPC sections 4.2, 5.2 and 5.1).

In vitro studies indicate that Tookad is unlikely to be a substrate of OATP1B1, OATP1B3, OCT1, OATP2B1, P-gp, BCRP, MRP2 or BSEP hepatic uptake transporters (see SmPC section 5.2). Uptake was shown to be partially increased in the presence of albumin and was temperature sensitive. It is suggested that the mechanism of uptake is via albumin receptors on the cells or via passive endocytosis and uptake into liver cells and hepatocytes (Mazor O, et al, Photochemistry and Photobiology 2005). These pathways are recognised but are considered to be of relatively low capacity.

Tookad was initially shown to be an inhibitor of OATP1B1 and 1B3 and several CYPs. However, updated *in vitro* results showed no inhibition of CYP enzymes when WST11 is protected from light, suggesting no inhibition of cytochrome P450s. Since this closely mimics the clinical situation the updated results are considered more reliable in the perspective of a risk assessment. A time dependency *in vitro* study showed some inhibition with a pre-incubation, but in the absence of NADPH the inhibition, even with a 30 min incubation, was less than 40% at the highest concentration of 5 µM. Therefore, Tookad at therapeutic concentrations is unlikely to inhibit cytochrome P450 enzymes but could inhibit both OATP1B1 and OATP1B3 transporters. The magnitude of interaction has not been investigated clinically but a transient increase in the plasma concentration of co-administered substrates of OATP1B1 and OATP1B3 cannot be ruled out. The use of medicinal products that are substrates of OATP1B1 or OATP1B3 (repaglinide, atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, bosentan, glyburide) for which concentration-dependent serious adverse events have been observed should be avoided on the day of Tookad infusion and for at least 24 hours after administration. Co-administration should be done with caution and close monitoring is recommended (see sections 4.5 and 5.2).

In vitro studies also indicate that Tookad does not inhibit P-gp, OAT1, OAT3, OCT2, OCT1, BCRP and BSEP (see sections 4.5 and 5.2).

The applicant has proposed a plausible mechanism of action for Tookad VTP. Erythrocyte aggregation has been described leading to blood clots at the interface of the arterial supply and tumour microcirculation, resulting in permanent occlusion of the entire tumour vasculature including the rim. Tumour necrosis results from a mixture of a coagulative process and endothelial cell apoptosis induced by reactive nitrogen species. In theory, vessel obstruction is confined to the tumour vascular bed due to the PK of WST11 with minimal tissue extravasation and fast clearance from the circulation. Free radicals are generated and react locally; the mean depth of necrosis visible on contrast enhanced MRI following Tookad VTP was 6 mm. Tookad showed weak clastogenic activity when activated by UV light. There was no evidence of increased neoplasia in the general toxicology studies with treatment administered over 14 days (see non-clinical data). Tookad is expected to be given once to patients. Furthermore, there currently is insufficient evidence to add this risk as an important potential risk in the RMP.

Taking into account the mechanism of action and absence of surrogate markers, the applicant could not identify any direct pharmacodynamic effects purely due to Tookad to correlate with PK. The applicant used surrogate markers to assess the PD effect of the Tookad: light combination, namely MRI scans and histopathology review. The closest correlate to a PD marker is probably the Day 7 percentage necrosis on the MRI scans. Necrosis was observed by MRI at day 7 in patients with localised prostate cancer who received Tookad VTP. There was a correlation between the total energy delivered and the volume of necrosis observed at day 7 (see SmPC section 5.1). Mean Day 7 percentage necrosis was higher with 4 mg/kg Tookad than 2 mg/kg but in the patients treated with 6 mg/kg Tookad there was no increase above that seen with 4 mg/kg. Higher percentage prostate necrosis was also linked to greater extra-prostatic necrosis.

A LDI ≥1 was determined as optimal for achieving adequate prostate necrosis. Based on results from study PCM202, it appeared associated with a greater volume of necrosis on Day 7 MRI and greater share of patients with negative biopsy at 6 months (see Clinical efficacy data and SmPC section 5.1). LDI ≥1 is thus an important predictor of outcome and treatment should not be undertaken in patients where an LDI ≥ 1 cannot be achieved (see section 5.1). There was no significant correlation between the percentage of prostate necrosis on Day 7 MRI and the likelihood of a negative prostate biopsy at follow-up.

Based on the results of the three phase 2 studies, the optimal treatment parameters were determined as a dose of 4 mg/kg dose of Tookad, a light energy of 200 J/cm and a minimum of 1 for the LDI. This is considered acceptable.

An LDI ≥1 was achieved for most patients in the Phase III study on initial treatment and also on first treatment of the contralateral lobe. An LDI ≥1 was possible in most patients with bigger prostates, involving more fibres and a longer procedure (see results under clinical efficacy). To ensure efficacy, during the procedure the number and the length of the optical fibres are selected depending on the shape and the size of the prostate and the optical fibres are positioned transperineally into the prostate gland under ultrasound guidance to achieve a Light Density Index (LDI) ≥ 1 in the targeted tissue. Planning of optical fibre positioning should be performed at the beginning of the procedure using the treatment guidance software.

An LDI ≥1 was rarely achieved on retreatment (27.3% of cases). It was postulated that due to fibrosis a lower LDI might be sufficient in these cases. This is speculative and it could equally be hypothesised that fibrotic tissue would require a higher LDI. Insufficient patients underwent retreatment of the ipsilateral lobe or sequential treatment of the contralateral lobe to determine the efficacy and safety of a second Tookad VTP procedure (see SmPC section 4.4). Retreatment is thus not recommended.

A whole lobe treatment of the prostate is appropriate as the disease can be accurately located anatomically; graded histologically and all involved areas of the prostate can be targeted. The 5 mm security margin for fibre placement is included in the treatment volume. In addition, significant protection to the nerve bundles is provided by the prostatic fascia. In the PCM301 study no patient was excluded based on the location of the tumour at baseline. Although the study was not designed to identify the impact of tumour location, an analysis of the outcomes based on the location of the tumour(s) at baseline, Month 12 and Month 24 showed a well-balanced distribution of the tumours within the apex, the median zone and the base (data not shown). The biopsy results and genitourinary adverse events, based on the location of positive biopsies at baseline, have shown comparable results (data not shown). A statement has been included in the SmPC to inform that before treatment, the tumour must be accurately located and confirmed as unilateral using high resolution biopsy strategies based on current best practice, such as multi-parametric MRI based strategies or template-based biopsy procedures. (see SmPC section 4.4).

There is limited biopsy data beyond 2 years after Tookad treatment, so long-term efficacy has not been determined. Residual tumour has been found on follow-up biopsy of the treated lobe at 12 and 24 months, usually outside of the treated volume, but occasionally within the area of necrosis. There is limited data on long-term outcomes and on potential consequences of post- Tookad local scarring in case of disease progression. At present Tookad -VTP has been shown to defer the need for radical therapy and its associated toxicity. Longer follow-up will be required to determine whether Tookad -VTP will be curative in a proportion of patients (see SmPC section 4.4).

Following Tookad VTP, patients should undergo digital rectal examination (DRE) and have their serum PSA monitored, including an assessment of PSA dynamics (PSA doubling time and PSA velocity). PSA should be tested every 3 months for first 2 years post VTP and every 6-month thereafter in order to assess PSA dynamics (PSA Doubling Time (DT), PSA velocity). Digital Rectal Examination (DRE) is recommended to be performed at least once a year and more often if clinically justified. Routine biopsy is recommended at 2-4 years and 7 years post VTP, with additional biopsies based on clinical/ PSA assessment. mpMRI may be used to improve the decision making but not, at present, to replace biopsy.

The safety and efficacy of subsequent radical therapy (surgery or radiotherapy) is uncertain. Limited information is available regarding the safety and efficacy of radical prostatectomy after Tookad -VTP. In small surgical series, there have been reports of T3 tumours, positive margins and impotence. In the 24 months of the pivotal European Phase III study, no patients underwent radical radiotherapy post Tookad -VTP (see SmPC section 4.4).

Considering the treatment might have implications for later radical treatment, post-operative histology should be reviewed and radiotherapy outcomes collected. A post-authorisation efficacy study (PAES: study CLIN1501 PCM401) with a 7-year follow up period will be conducted to collect this information and is included as a condition in Annex II of the opinion. This study is considered adequate to assess the long term efficacy of Tookad. The study will also collect safety data and is reflected in the RMP (see clinical safety and RMP section). Tumour location in relation to toxicity and oncological outcome will be captured. Further long-term efficacy and safety will also be provided from study PCM301 FU5 (see discussion on clinical efficacy, Annex II and RMP).

Furthermore, the effect of causing blood vessel occlusion on the ability to later treat patients with surgery or radiotherapy will be monitored by additional pharmacovigilance (see clinical safety and RMP).

There is a risk of skin and eye photosensitivity with exposure to light post Tookad -VTP. The advice regarding phototoxicity (duration of protection from light) is justified, based on the very short plasmatic half-life, absence of skin (or eye) accumulation, dosing for prostate cancer (4mg/kg) below the minimum dose that tested positive in skin photosensitization testing, ophthalmologic examination and the absence of photosensitization events in the clinical development.

It is important that all patients follow the light precautions below for 48 hours post-procedure to minimize the risk of damage to the skin and eyes. Patients should avoid exposure to direct sunlight (including through windows) and all bright light sources, both indoors and outdoors. This includes sunbeds, bright computer monitor screens and medical examination lights, such as ophthalmoscopes, otoscopes and endoscopy equipment, for 48 hours following the VTP procedure.

Sunscreen creams do not protect against near infra-red light and, therefore, do not provide adequate protection.

If the patient reports discomfort to the skin or eyes during hospitalisation, reduce the level of lighting and take extra care to shield the patient from artificial and natural light.

During the first 12 hours after VTP procedure, the patient should wear protective goggles and be kept under medical surveillance for at least 6 hours in a room with dimmed light.

The patient may be discharged in the evening of the same day at the physician's discretion.

The patient must stay in a dimmed light environment without any direct exposure of the skin and the eyes to daylight. The patient may only use incandescent light bulbs with a maximum power of 60 watts or equivalent (i.e. 6 watts for LED lights, 12 watts for fluorescent low-energy lights).

The patient may watch television from a distance of 2 metres and, from 6 hours onwards, may use electronic devices such as smartphones, tablets and computers. If the patient must go outdoors during daylight hours, he should wear protective clothes and high protection goggles to shield his skin and eyes.

During 12-48 hours after VTP procedure, the patient may go outdoors during daylight hours but only in shaded areas or when it is overcast. He should wear dark clothes and take care when exposing hands and face to the sun. The patient can return to normal activity and tolerate direct sunlight 48 hours after the procedure. No patients with photosensitive dermatitis, skin conditions such as porphyria or a history of sensitivity to sunlight have received Tookad in clinical studies. However, the short duration of action of Tookad means that the risk of enhanced phototoxicity is expected to be low provided these patients strictly follow the precautions against light exposure. There could be an additional risk of eye photosensitivity in patients who have received intra-ocular anti-VEGF therapy. Patients who have received prior VEGF therapy should take particular care to protect the eyes from light for 48 hours post Tookad injection. Concomitant use of systemic VEGF inhibitors is not recommended with Tookad.

In studies of Tookad in age related macular degeneration, three cases of retinal artery occlusion occurred with an increased risk in patients with previous therapy with antiangiogenic agents; these would have been administered inter-ocularly. With 4 mg/kg Tookad, the photosensitisation period is limited to 6 hours post dosing and advice is given regarding light exposure is to minimise the risk of ocular toxicity.

There is a potential for interaction with other drugs that have photosensitising effects. Medicinal products which have potential photosensitising effects (such as tetracyclines, sulphonamides, quinolones, phenothiazines, sulfonylurea hypoglycaemic agents, thiazide diuretics, griseofulvin or amiodarone) should be stopped at least 10 days before the procedure with Tookad and for at least 3 days after the procedure or replaced by other treatments without photosensitizing properties. If it is not possible to stop a photosensitising medicinal product (such as amiodarone), the patient should be advised that increased sensitivity to sunlight may occur and they may need to protect themselves from direct light exposure for a longer period (see SmPC section 4.5).

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of padeliporfin for the current application are well characterized, and well described in the SmPC. The mode of action of Tookad was supported by literature data. The tumour must be accurately located and confirmed as unilateral using high resolution biopsy strategies based on current best practice, before treatment with Tookad. The risk of effects outside the prostate, both local and systemic, and the potential for drug-drug interactions appears low and adequate recommendations have been included in the SmPC. Considering the lack of long-term data, two PAES studies will be conducted to assess long term efficacy and safety of Tookad, in particular, evaluating the potential impact on subsequent radical therapy (see discussion on clinical efficacy and safety).

2.5. Clinical efficacy

2.5.1. Dose response studies

Three Phase II trials for prostate cancer were provided in which three doses of Tookad (2, 4 and 6 mg/kg) and two 753 nm light doses (200 and 300 Joules/cm of fibre) were tested. Based on the results, the following treatment parameters were considered optimal: 4 mg/kg dose of Tookad with a light energy of 200 J/cm and a minimum of 1 for the LDI. In addition to the dose and light energy the number of fibres and size of the prostate has to be taken into account. These studies are described and discussed under the section on pharmacology.

2.5.2. Main study

CLIN 1001 PCM301

The main study is a randomized phase III trial to assess the efficacy and safety of Tookad VPT for Localised Prostate Cancer *versus* active surveillance in localised prostate cancer (PCM 301) Compared to Active Surveillance.

Methods

Study Participants

Main **inclusion** criteria:

1. Men with previously untreated low-risk localised prostate cancer diagnosed by transrectal ultrasound (TRUS)-guided biopsy from 10 to 24 cores performed less than 12 months prior to enrolment (biopsy criteria updated in protocol versions 3.0 and 4.0)
   - 2 to 3 cores positive for cancer; subjects with 1 positive core allowable if at least 3 mm of cancer core length
   - maximum Gleason score of 3 + 3
   - maximum cancer core length of 5 mm in any core
2. Cancer clinical stage up to T2a
3. PSA ≤ 10 ng/mL (≤5 ng/mL for subjects using a 5-α-reductase inhibitor [5–ARIs])

4. Prostate volume ≥ 25 cc and < 70 cc.

Main **exclusion** criteria:

1. Unwillingness to accept randomisation to either of the study arms
2. Any prior or current prostate cancer treatment, including surgery, radiation therapy (external or brachytherapy) or chemotherapy
3. Any surgical intervention for benign prostatic hypertrophy (added in protocol Version 6.0)
4. Life expectancy < 10 years
5. Contra-indication to magnetic resonance imaging (MRI) (e.g. pacemaker, history of allergic reaction to gadolinium) or factors preventing accurate reading of pelvic MRI (e.g. hip prosthesis)
6. Any condition or history of illness or surgery that may pose an additional risk to men undergoing the Tookad Soluble VTP procedure such as:

a. Medical conditions that preclude a general anaesthetic

b. History of active rectal inflammatory bowel disease or other factors which may increase the risk of fistula formation

c. Hormonal manipulation (excluding 5-ARIs) or androgen supplements in the previous 6 months

d. History of urethral stricture disease

e. History of acute urinary retention within 6 months of study entry

f. Medical conditions that need medication with potential photosensitising effects (e.g. tetracyclines, sulphonamides, phenothiazines, sulfonylurea hypoglycaemic agents, thiazide diuretics, griseofulvin and amiodarone) if these treatments cannot be stopped or replaced

g. Absolute need for anticoagulant drugs or antiplatelet drugs (e.g. warfarin, aspirin) that cannot be withdrawn during the 10 days prior to the Tookad Soluble VTP procedure

h. Renal and hepatic disorders with values of > 1.5 times the upper limit of normal and blood disorders (clinician judgement)

i. History of sun hypersensitivity or photosensitive dermatitis

Treatments

Tookad soluble VTP:

Under general anaesthetic, transparent guidance needles were positioned in the prostate gland to allow coverage of the desired treatment zone while sparing surrounding tissues with a margin of at least 5 mm between the fibres and the rectal wall, prostate apex and urethra.

Once the interstitial optical fibres were accurately positioned in the prostate gland to cover the desired treatment zone, a single 10-minute intravenous (IV) infusion of 4 mg/kg Tookad was administered. The drug was activated in the predetermined treatment zone by local illumination with laser light at 753 nm with a fixed power of 150mW/cm over 22 minutes and 15 seconds, corresponding to an energy dose of 200 J/cm.

In case of unilateral disease, focal treatment of one lobe was to be applied. In case of bilateral disease (discovered at entry or during follow-up), bilateral treatment was to be applied, either simultaneously or consecutively. Retreatment of lobes found positive for cancer at 12 months follow-up was allowed.

The subjects were kept under medical surveillance in dimmed light for at least 6 hours post procedure and discharged from hospital either the same evening or the following day.

Active surveillance:

Active surveillance was conducted in line with existing recommendations (Mottet et al., 2015; American Urological Association Clinically Localized Prostate Cancer: 2007 Update).

Active surveillance included deferral of active treatment and periodic monitoring with prostate-specific antigen (PSA) tests at 3 monthly intervals, physical examinations and annual prostate biopsy. It involved serial absolute PSA measurements and ultrasound-guided prostatic biospy at 12 and 24 months.

Follow-up

Subjects in both treatment groups were followed for approximately 24 months after randomisation and underwent the same efficacy and safety assessments. A TRUS-guided biopsy of 10 to 24 cores was performed at Month 12 and Month 24. PSA was measured and digital rectal examination (DRE) was performed every 3 months.

Prior and concomitant therapy

The following medications were prohibited from 10 days before to 3 days after the procedure: Medications with potential photosynthesising effects, Anticoagulants, Compounds that decrease clotting, vasoconstriction and platelet aggregation (e.g. aspirin). Prolonged 5-ARI use decreases serum PSA levels; a subject on a 5-ARI for over 6 months was not to adjust 5-ARI therapy during the study. Enrolment of a subject who had started 5-ARI therapy within 6 months was to be discussed with the Medical Monitor before randomisation.

Thromboembolic prophylaxis was instigated as per local clinical standards.

Objectives

The co – primary objectives were:

A. To assess the impact of Tookad VTP on the rate of absence of definite cancer using patients on active surveillance as a comparison, measured as absence of any histology result definitively positive for cancer at 24 months

B. To determine the difference in rate of treatment failure associated with observed progression of disease from low risk prostate cancer to moderate or higher risk prostate cancer in men who undergo Tookad VTP compared to men on active surveillance.

Secondary objectives were:

To determine the differences between men who undergo Tookad Soluble VTP and men on active surveillance with regard to:

- total cancer burden in the prostate (total number of positive cores)
- rate of additional prostate cancer radical therapy including surgery, radiotherapy [external beam, brachytherapy], high-intensity focused ultrasound, cryotherapy, hormonal therapy or chemotherapy
- rate of severe prostate cancer-related events: cancer extension to T3, metastasis and prostate cancer-related death
- rate of adverse events (AEs)
- rate of incontinence, erectile dysfunction and urinary symptoms

The overall quality of life was recorded for potential utility and descriptive studies. Overall quality of life was recorded using the IPSS and IIEF-15 questionnaires administered every 3 months until Month 12 and at Month 24 and 7 days post-treatment for subjects administered Tookad. The EQ-5D questionnaire was administered at Month 12 and 24.

Outcomes/endpoints

The primary efficacy endpoints were defined as follows:

- Co-primary endpoint A: Rate of absence of definitive cancer: Absence of any histology result definitively positive for cancer at 24 months
- Co-primary endpoint B: Rate of treatment failure associated with observed progression of cancer from low to moderate or higher risk over the 24 months of follow-up. Moderate or higher risk is defined as the observation of 1 of the following events:
    - More than 3 cores definitively positive for cancer when considering all histological results available during follow-up in the study
    - Any Gleason primary or secondary pattern of 4 or more
    - At least 1 cancer core length > 5 mm
    - PSA > 10 ng/mL in 3 consecutive measures
    - Any T3 prostate cancer
    - Metastasis
    - Prostate cancer-related death

For both co-primary endpoints, the blinded adjudication of the biopsy results by the Outcomes Review Panel (ORP), taking into account the local and centralised pathology evaluations, was the basis for analysis.

The secondary efficacy endpoints were defined as follows:

- Total number of cores positive for cancer: The total number of positive cores observed during follow-up is calculated, for each biopsy, by adding the number of positive cores observed in each of the right and left lobes.
- Notification of initiation of any radical therapy (any radical treatment for prostate cancer other than the treatment to which the subject was randomised, including surgery, radiotherapy [external beam, brachytherapy, focused], high-intensity focused ultrasound, cryotherapy, hormonal therapy for cancer, or chemotherapy for cancer)

- Proportion of subjects with a severe prostate cancer-related event: cancer extension to T3, metastasis, or prostate cancer-related death

Post-treatment mpMRI was performed 7 days after the Tookad VTP procedure. Patients in both treatment groups were followed for approximately 24 months after randomisation and underwent the same efficacy and safety assessments. A TRUS-guided biopsy of 10 to 24 cores was performed at Month 12 and Month 24. The ORP, an independent and blinded panel of experts, reviewed all reports of TRUS-guided biopsy for all subjects (Selection, Month 12, Month 24) and any other pathological report available at any time during the follow-up period to determine the number of cores positive for cancer observed in these histological reports and their likely location within the prostate per lobe. The Month 12 and Month 24 biopsies were read centrally by an independent pathologist, blinded to the treatment assignment and to the local pathologist reading, and all the cases for which this reading was discrepant with the local pathologist reading were adjudicated by the ORP pathologist. Any additional radical prostate cancer treatments, metastases, evidence of T3 disease, and severe prostate cancer-related events were recorded at Month 12 and Month 24. PSA was measured and digital rectal examination was performed every 3 months.

At the end of the study, patients were eligible for entry into a long-term follow-up programme (Study PCM301 FU5), in which outcomes are being recorded for a further 5 years.

Sample size

The following assumptions were made to calculate the sample size for co-primary-endpoint B:

- The proportion of patients with a failure at 2 years will be 15% in the active surveillance group and 5% in the Tookad Soluble VTP arm (a hazard ratio of 0.32 in favour of the intervention)
- For the purposes of sample size calculation, the two-sided significance level is taken equal to 0.025 to account for the fact that two co-primary endpoints will be tested; however, the analysis of each co-primary endpoint will be carried out at the 0.05 significance level with a Hochberg procedure to control for multiplicity
- The power required for each co-primary endpoint is 80%

For co-primary endpoint B, with these assumptions, the total sample size required is 400 patients (200 patients per arm), and at least 40 events (patients with disease progression) need to be observed for the final analysis to take place.

With this number of patients, the comparison of the two randomized groups will have > 99.9% power to detect the expected difference for co-primary endpoint A, since the absence of any histology result definitely positive for cancer 24 months after the intervention is expected to exceed 70% in the intervention arm vs. at most 30% in the control arm (false negative biopsies). Assuming that at least 150 patients will be evaluable for the biopsy at 24 months in the intervention arm, the rate of negative biopsies will be estimated with a standard error of less than 4%.

Randomisation

Eligible patients were individually randomised to Tookad VTP or Active Surveillance with a 1:1 ratio. Central randomisation was performed using an independent web-based allocation system. Randomisation was stratified by centre using balanced blocks of variable size.

Blinding (masking)

This is an open-label study.

Blinding was applied to outcomes evaluation and statistical treatment.

Statistical methods

Analyses were described prospectively in the Statistical Analysis Plan (SAP) dated 21.11.14. All analyses were performed using SAS Version 9.3 or higher. All statistical tests were 2-sided and at a 5% level of significance.

The following analysis populations were defined:

- Intention-To-Treat (ITT): includes all randomised subjects, analysed as randomised.
- Modified Intention-To-Treat (mITT): includes all subjects in the ITT population randomised to the Tookad Soluble VTP group who received any amount of Tookad Soluble or initiated any study treatment-related procedure (including anaesthesia) and all subjects in the ITT population randomised to the active surveillance group. Subjects were analysed as randomised.
- Per-protocol (PP): includes all subjects in the ITT population, randomised to either group, who had no major protocol violations. The PP population will consist of all subjects who met the following criteria:
    - Complied with the protocol for inclusion and exclusion criteria and follow-up
    - Received the appropriate dose of Tookad Soluble and energy delivered and underwent VTP
    - Had no major protocol deviations. The list of subjects excluded from the PP population was identified during the data review meeting and approved before database lock.

The ITT population was used for all demographic and efficacy endpoints, the mITT and the PP populations were used for primary efficacy endpoints.

The **co-primary efficacy endpoints** were analysed as follows:

- Co-primary endpoint A was analysed as a dichotomous outcome, i.e. success (absence of any histology result definitely positive for cancer) or failure (presence of at least 1 result definitely positive for cancer). Subjects who dropped out before Month 3 or before Tookad administration were counted as failures. Subjects who dropped out between Months 3 and 24 were asked to undergo a biopsy at Month 24. A subject who did not undergo the Month 24 biopsy was counted as a failure. Proportions of subjects with observed success were compared between the 2 treatment arms using a 2-sided Pearson's chi-square test. The crude odds ratio and the risk ratio at 24 months, comparing Tookad versus active surveillance and the associated 95% confidence interval (CI), were presented.
- Co-primary endpoint B was analysed using survival analysis methods. The event was progression, defined as the first occurrence of an exam meeting the criteria for progression to moderate- or higher-risk cancer. Distribution of events occurring over time during follow-up was estimated using the Kaplan-Meier method. The estimated progression rates and associated 95% CI were presented at Months 6, 12, 18 and 24. Time to progression was compared between the 2 treatment groups using the log-rank test. The crude hazard ratio at 24 months comparing Tookad versus active surveillance and the associated 95% CI was presented, using a Cox proportional hazards regression model.

The Hochberg procedure was used to adjust for multiplicity of the 2 co-primary endpoints.

Sensitivity analyses

Sensitivity analyses included parametric estimations of time to progression for the ITT. Adjusted analyses for both co-primary endpoints were conducted.

Multivariate modelling using a logistic regression was applied. The regression model incorporated Baseline assessment of age, number of positive cores, prostate volume and disease status (unilateral or bilateral) in addition to treatment to provide an adjusted comparison of the 2 treatment groups with respect to probability of success/failure for co-primary endpoint A and the HR of progression for co-primary endpoint B. In the Cox model analysis, the proportional hazard assumption was checked graphically plotting the log(-log[survival]) and was to be relaxed if necessary.

For co-primary endpoint B, subjects who withdrew from the study or opted for radical treatment before prostate cancer progression were censored. A sensitivity analysis, using a Cox proportional hazards model, assumed these subjects to be failures (defined as worst-case scenario in the SAP).

Biopsies were performed according to a predefined visit schedule (interval-censored data). Simplified Kaplan Meier curves were constructed by rounding the recorded visit times to the closest 6-monthly visit time point to improve visual interpretation.

The **secondary efficacy endpoints** were analysed as follows:

The total number of positive cores for both lobes was calculated for each follow-up biopsy and the mean total was compared between the 2 treatment groups using a Student *t* test. The mean maximum cancer core length was compared between the 2 treatment groups at Month 12 and Month 24 using a Student *t* test. In addition, the number and percentage of subjects with a maximum cancer core length ≥ 5 mm or < 5 mm at Months 12 and 24 were presented by treatment group.

The time to initiation of radical therapy was estimated using the Kaplan-Meier method. The log-rank test was used to compare the time to initiation of radical therapy between the 2 treatment groups. Subjects who did not initiate any radical therapy were censored at the time of study completion.

Descriptive statistics on incidence rates of severe cancer-related events (any T3 prostate cancer, metastasis or prostate cancer-related death) were reported.

For the questionnaires (IPSS, IIEF-15, EQ-5D), descriptive summaries of the raw score and change from Baseline at each time point were provided for observed cases and using a multiple imputation method. The difference between treatment groups in change from Baseline to Month 24 (imputed) was analysed using an analysis of covariance (ANCOVA) model with treatment group as the fixed effect and Baseline score as a covariate. ANCOVA adjusted mean change from Baseline of scores difference was provided along with standard error (SE) and 95% CI within each treatment group.

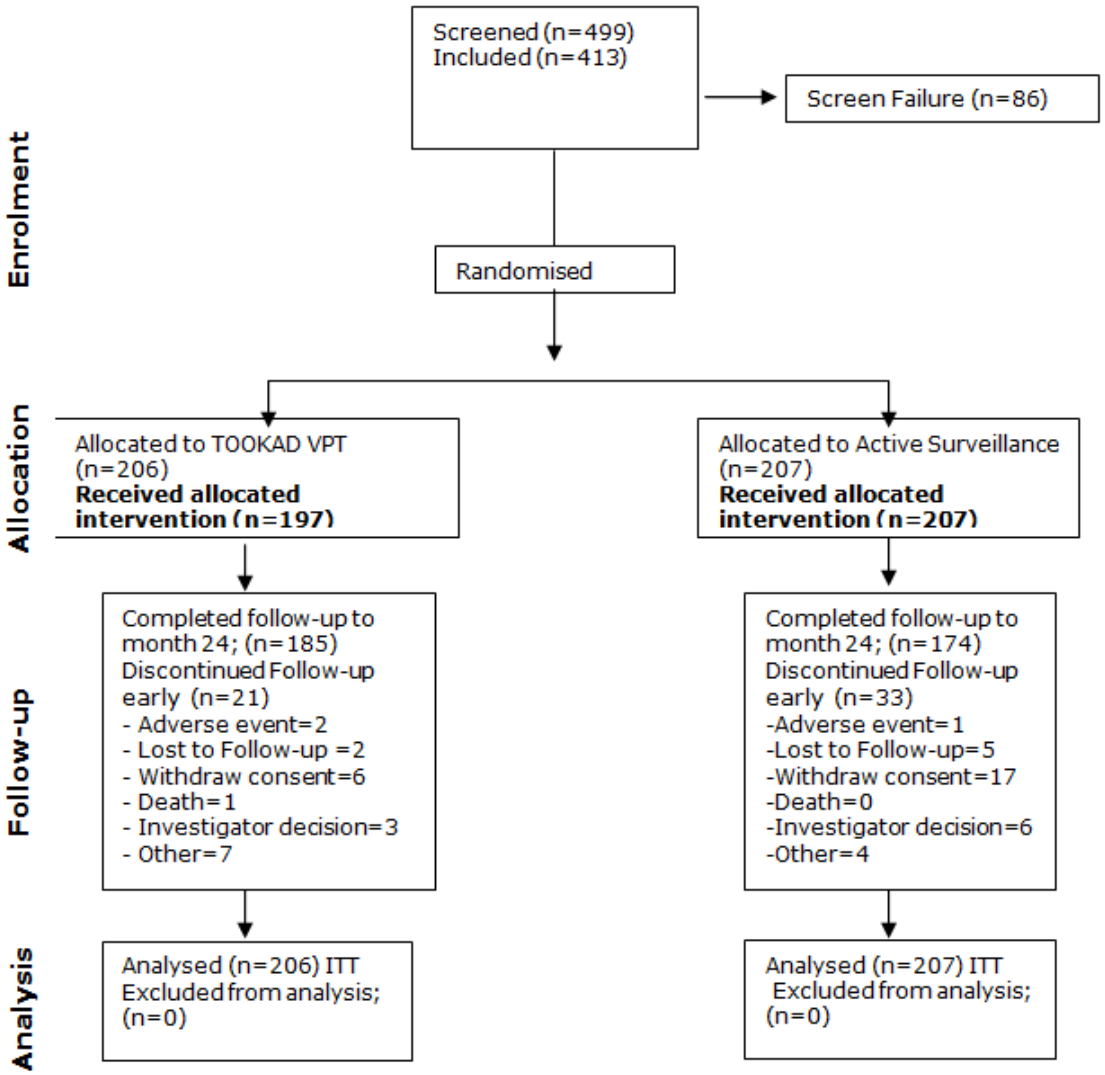
Exploratory and Additional Efficacy Analysis

Subjects who met the progression criteria at Month 12 were analysed as failure for the co-primary endpoint B in the primary analysis. A sensitivity analysis was performed using the status at Month 24 after retreatment or treatment of contralateral non-treated lobe to review the outcome of the Tookad Soluble VTP strategy, including retreatment.

Also, both co-primary endpoints were evaluated using only data from assessments performed on the treated lobe(s) for the Tookad group and lobe(s) with disease at Baseline for the active surveillance group. A subgroup efficacy analysis was performed by disease status at Baseline (unilateral or bilateral).

Results

Participant flow



There were 86 screen failures, most of them because the biopsy did not show low risk prostate cancer or the PSA was above 10ng/mL; 11 patients were excluded because their prostate was not in the range 25-70cc.

Recruitment

The study was conducted between 8 March 2011 and 25 June 2015. From the 8th March 2011, a total of 413 men diagnosed with low-risk prostate cancer by transrectal ultrasound (TRUS)-guided biopsy with no prior treatment for prostate cancer were screened and randomized.

Fifty-nine hospitals were initiated for this study and 47 centres in Belgium, Finland, France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland and the United Kingdom enrolled subjects.

Conduct of the study

Protocol changes

The original protocol was version 2.1 (January 2011). Version 2.2 (April 2011) updated study personnel and the definition of adverse events.

Changes (version 3, August 2011; version 4, November 2011 and version 5, June 2012) mainly concerned the type and numbers of prostate biopsies required (from 2 sets of 12 core biopsies or a 24 core saturation biopsy to one 12 [±2] core biopsy) and the time from biopsy to enrolment in order to simplify the entry criteria, accommodate the standard of care in different countries and facilitate recruitment.

Protocol version 6.0 (23 October 2012) added 'any surgical intervention for benign prostatic hypertrophy' as an exclusion criterion. The rationale was that altered prostatic anatomy would make the accurate placement of the illuminating fibres more difficult and potentially increase the risk of extra -prostatic illumination with possible necrosis of the urinary sphincter, the neurovascular bundles or the rectal wall.

The statistical analysis plan includes 2 changes from the analyses planned in the protocol:

The safety population was modified to include subjects who initiated any study treatment-related procedure (including anaesthesia) in the safety analyses.

The definition of emergent AEs was modified to start after randomisation. Because subjects in the active surveillance group were given no treatment after randomisation while the Tookad Soluble VTP procedure might have taken place several weeks after randomisation, this change provided comparable periods of AE collection between the 2 treatment groups.

Protocol violations

There were 39 major deviations in the VTP and 26 in the active surveillance group. Most major deviations in the VTP group were due to not receiving any Tookad or an inappropriate dose/ energy delivered. In addition, 11 patients with bilateral disease were treated in only 1 lobe. The month 24 biopsy was not performed in about 11% of patients, not previously classified as treatment failures.

There were 114 minor protocol deviations, mainly VTP not being performed according to the guidelines. These were stated as minor modifications to the number and length of fibres due to the prostate volume and shape.

Baseline data

Table 22 Demographic and baseline disease characteristics by treatment group – ITT population (Study PCM 301)

Characteristic	VTP N = 206	Active Surveillance N = 207	Total N = 413
Age (years)[a]			
Mean (SD)	64.2 (6.70)	62.9 (6.68)	63.5 (6.71)
Range: minimum, maximum	45, 85	44, 79	44, 85
Race			
Caucasian, n (%)	202 (98.1)	206 (99.5)	408 (98.8)
Black, n (%)	3 (1.5)	0	3 (0.7)
Asian, n (%)	0	1 (0.5)	1 (0.2)
Other, n (%)	1 (0.5)	0	1 (0.2)
Body mass index (kg/m^2)			
Mean (SD)	26.47 (3.337)	27.34 (3.947)	26.91 (3.677)
Range: minimum, maximum	18.8, 38.6	18.8, 44.8	18.8, 44.8

Abbreviations: SD = standard deviation; VTP = vascular-targeted photodynamic therapy.
[a] $p = 0.051$ from Student t test
Sources: Table 14.1.5; Listing 16.2.4.

Characteristic	VTP N = 206	Active Surveillance N = 207	Total N = 413
Time since diagnosis (months)			
Mean (SD)	6.34 (8.536)	6.02 (7.887)	6.18 (8.209)
Range: minimum, maximum	0.2, 54.2	0.2, 47.4	0.2, 54.2
TNM staging			
T1a, n (%)	1 (0.5)	0	1 (0.2)
T1c, n (%)	177 (85.9)	180 (87.0)	357 (86.4)
T2a, n (%)	28 (13.6)	27 (13.0)	55 (13.3)
PSA (ng/mL)			
Mean (SD)	6.19 (2.114)	5.91 (2.049)	6.05 (2.084)
Range: minimum, maximum	0.1, 10.0	0.5, 10.0	0.1, 10.0
Estimated prostate volume (cc)[a]			
Mean (SD)	42.5 (12.49)	42.5 (11.76)	42.5 (12.11)
Range: minimum, maximum	25, 70	25, 70	25, 70
Unilateral disease, n (%)	157 (76.2)	163 (78.7)	320 (77.5)
Bilateral disease, n (%)	49 (23.8)	44 (21.3)	93 (22.5)
Total number of cores			
Mean (SD)	13.6 (3.31)	13.6 (3.55)	13.6 (3.43)
Range: minimum, maximum	10, 25	10, 26	10, 26
Total number of positive cores[b]			
Mean (SD)	2.1 (0.68)	2.0 (0.72)	2.1 (0.70)
Range: minimum, maximum	1, 3	1, 3	1, 3
1 positive core, n (%)	39 (18.9)	52 (25.1)	91 (22.0)
2 positive cores, n (%)	110 (53.4)	100 (48.3)	210 (50.8)
3 positive cores, n (%)	57 (27.7)	55 (26.6)	112 (27.1)
Total cancer core length (mm)			
Mean (SD)	4.3 (2.31)	3.8 (2.40)	4.1 (2.37)
Range: minimum, maximum	0[c], 14	0[c], 11	0,14

Abbreviations: SD = standard deviation; TNM = tumour, nodes, metastasis; VTP = vascular-targeted photodynamic therapy.
[a] $p = 0.995$ from Student t test
[b] $p = 0.291$ from Student t test
[c] Some of the subjects included on the basis of 2 biopsies at the beginning of the study had 1 of those 2 biopsies negative.
Sources: Table 14.1.6; Listings 16.4.2, 16.4.4.

Four patients had already undergone a prostatectomy (3 in the VTP and 1 in the active surveillance group); they were enrolled before this became an exclusion criterion (protocol version 6.0).

All patients had Gleason score ≤ 3 + 3 at baseline.

There were 6 patients (2.9%) aged > 75 years in each group.

Numbers analysed

Table 23 Analysis Populations by Treatment Group- all randomised subjects PCM 301

Analysis Population	VTP N = 206, n (%)	Active Surveillance N = 207, n (%)	Total N = 413, n (%)
Intention-to-treat	206 (100)	207 (100)	413 (100)
Modified intention-to-treat	197 (95.6)	207 (100)	404 (97.8)
Per-protocol	167 (81.1)	181 (87.4)	348 (84.3)
Safety	197 (95.6)	207 (100)	404 (97.8)

The 9 subjects in the VTP group excluded from the mITT and safety populations did not receive any Tookad or initiate any study treatment-related procedure (including anaesthesia) for the following reasons: withdrew consent after randomisation (3), discontinued by the Investigator for non-compliance (1), myocardial infarction (1), bladder cancer discovered on pre-treatment MRI (1), history of TURP- exclusion criterion (1), previous Gleason 3+4 biopsy - exclusion criterion (1) and unable to undergo pre-treatment MRI due to claustrophobia (1).

One subject had an anaphylactic reaction to the anaesthesia and did not receive any Tookad; he was included in the mITT and safety populations but not in the 196 subjects listed as receiving Tookad in the table below.

The PP population excluded the additional 30 patients in the VTP group (above the 9 subjects who did not receive any Tookad or initiate any treatment-related procedure) and the 26 in the active surveillance group who had major protocol violations.

Details of Tookad treatment

Of the 206 subjects randomised Tookad -VTP, 10 did not receive treatment for various reasons including study withdrawal, meeting exclusion criteria, non-compliance and other medical events.

Table 24 Treatment with Tookad Soluble VTP – Intention-to-Treat Population PCM301

Category	Disease Status at Selection		Total VTP N = 206, n (%)
	Unilateral N = 157, n (%)	Bilateral N = 49, n (%)	
Did not receive any treatment	6 (3.8)	4 (8.2)	10 (4.9)
Unilateral treatment before Month 12	151 (96.2)	12 (24.5)	163 (79.1)
Contralateral treatment before/ after Month 12 - sequential bilateral treatment before Month 12 -treatment of untreated contralateral lobe after Month 12	27 (17.2) 0 27 (17.2)	35 (71.4)[a] 33 (67.3) 2 (4.1)[a]	62 (30.1) 33 (16.0) 29 (14.1)
Treatment in previously treated lobe after Month 12	7 (4.5)	4 (8.2)[a]	11 (5.3)
Treatment in both lobes after Month 12	2 (1.3)	0	2 (1.0)

[a] The second procedure for Subject 25039-27 was incorrectly recorded in the eCRF as retreatment when it was a contralateral treatment. The results in this table include this procedure as contralateral treatment.

The 33 subjects with bilateral disease who received sequential treatment before 12 months had a mean interval of 7.9 months (range 5.8 – 12.4 months) between procedures.

Table 25 Tookad Soluble VTP Treatment Characteristics by Treatment - Intention-to-Treat Population PCM 301

Characteristic	First Treatment N = 196	Contralateral Treatment N = 62a	Retreatment N = 11a	Contralateral & Retreatment N = 2
Total fibre length (mm) Mean (SD) Range: minimum, maximum	 389.7 (124.84) 155, 910	 359.5 (141.94) 155, 870	 191.8 (87.19) 40, 340	 365.0 (120.21) 280, 450
Number of fibres used Mean (SD) Range: minimum, maximum	 12.9 (2.44) 6, 20	 13.3 (3.42) 7, 21	 11 (7.5) 3, 11	 16.0 (4.24) 13, 19
Energy applied (J) Mean (SD) Range: minimum, maximum	 7780.4 (2497.50) 3100, 18200	 7183.9 (2828.73) 3100, 17400	 3836.4 (1743.72) 800, 6800	 7300.0 (2404.16) 5600, 9000
Light density index < 1 (n, %) ≥ 1 (n, %)	 6 (3.1) 190 (96.9)	 0 62 (100)	 8 (72.7) 3 (27.3)	 1 (50.0) 1 (50.0)

a The second procedure for one subject was incorrectly recorded in the eCRF as retreatment when it was a contralateral treatment. The results in this table include this procedure as contralateral treatment.

Outcomes and estimation

Co-primary endpoint A: Absence of definitive cancer (defined as absence of any histological result definitely positive for cancer for subjects who have histology results)

Table 26 Biopsy Results in the whole prostate including untreated lobes Study PCM301 – ITT Population

Visit	Subjects with Negative Biopsy		VTP vs Active Surveillance		
	VTP N = 206 n (%)	Active Surveillance N = 207 n (%)	Risk Ratio (95% CI)	Odds Ratio (95% CI)	*p*-value[b]
Month 12 **Negative biopsy** **No biopsy** **Positive biopsy**	 98 (47.6) 14 (6.8) 94 (45.6)	 41 (19.8) 21 (10.1) 145 (70.0)	2.40 (1.76, 3.27)	3.67 (2.37, 5.69)	< 0.001
Month 24 **Negative biopsy** **No biopsy** Radical therapy Other[a] **Positive biopsy**	 101 (49.0) 38 (18.4) 12 (5.8) 26 (12.6) 67 (32.5)	 28 (13.5) 86 (41.5) 55 (26.6)[c] 31 (15.0) 93 (44.9)	3.62 (2.50, 5.26)	6.15 (3.79, 9.97)	< 0.001

[a] For example: study withdrawal, medical reason, subject refusal.
Subjects with missing biopsies are considered as failures.
[b] From Pearson's chi-square test for observed success
[c] Among the 60 patients who had radical therapy, 5 patients had a Month 24 biopsy

Co-primary endpoint B – Treatment failure (examination meeting the criteria for progression to moderate/ higher risk cancer)

Table 27 Progression by Treatment Group - Kaplan-Meier Analysis - ITT Population PCM301

	VTP N = 206 n (%)	**Active Surveillance N = 207 n (%)**
Median time to progression[a], months (95% CI)	28.3 (26.0, 30.6)	14.1 (12.9, 23.8)
Estimated proportion (95% CI) of subjects progressed by 6 months 12 months 18 months 24 months	 0.5 (0.1, 3.5) 7.2 (4.3, 11.8) 24.1 (18.6, 30.8) 27.1 (21.3, 34.1)	 2.5 (1.0, 5.9) 21.1 (16.0, 27.6) 53.3 (46.4, 60.6) 60.1 (53.1, 67.3)
p-value[b]	< 0.001	

[a] Calculated from the standard Kaplan-Meier curve (Figure 14.2.2.1.1)
[b] From the log-rank test of equality of survival curves across treatment groups

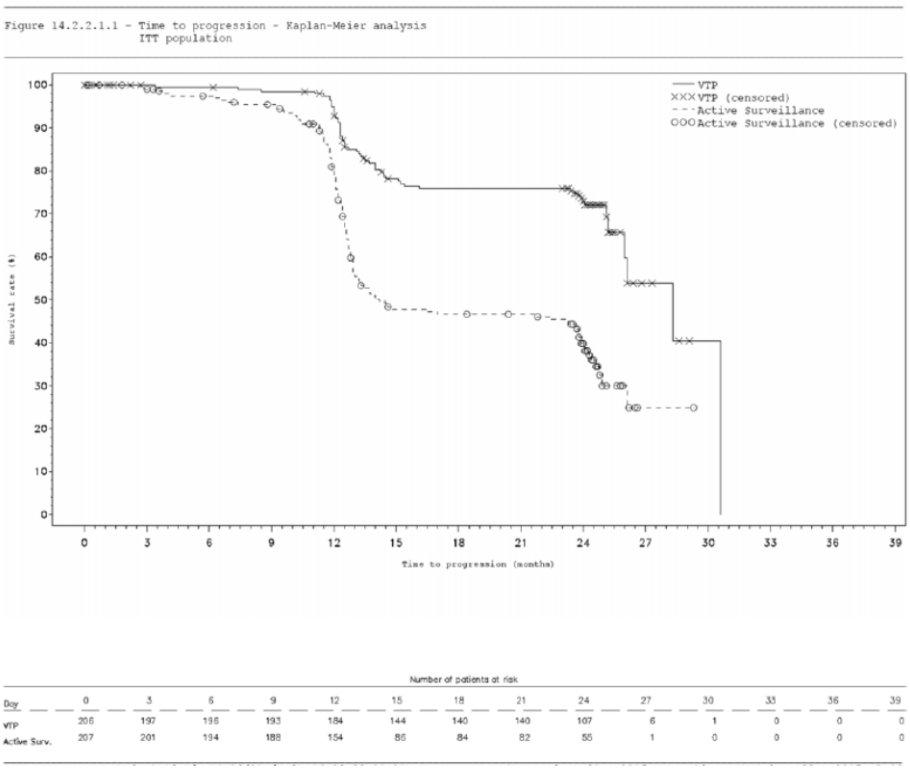


Figure 3 Time to progression – Kaplan Meier Analysis – ITT population

Table 28 Progression by Treatment Group- Observed Numbers (Proportion) of Events at Month 12 and Month 24 – Intention-to-Treat Population PCM301

Time Period – Category	VTP N = 206, n (%)	Active Surveillance N = 207, n (%)
Month 12		
Subjects with progression	44 (21.4)	98 (47.3)
Subjects without progression	148 (71.8)	88 (42.5)
Subjects with radical therapy leading to missing biopsy	0	4 (1.9)
Subjects with missing biopsies (other reasons)	14 (6.8)	17 (8.2)
Month 12 to Month 24		
Subjects with progression	22 (10.7)	53 (25.6)
Subjects without progression	147 (71.4)	71 (34.3)
Subjects with radical therapy leading to missing biopsy	11 (5.3)	56 (27.1)
Subjects with missing biopsies (other reasons)	26 (12.6)	27 (13.0)
Month 24 (Cumulative)		
Subjects with progression	58 (28.2)	120 (58.0)
Subjects with radical therapy leading to missing biopsy	11 (5.3)	56 (27.1)

Note: The number of subjects with radical therapy leading to missing biopsies by month 24 is not the full number of subjects with radical therapy. This analysis is described later as a secondary endpoint.

The proportion of patients who progressed over 24 months in the Tookad group was lower than that in the active surveillance group (28.2% vs. 58.0%, HR=0.34 [0.25, 0.47], log-rank p-value < 0.001).

Secondary efficacy endpoints

Initiation of Radical Therapy

Table 29 Time to initiation and Percentage of subjects who initiated Radical Therapy by Treatment Group – Kaplan- Meier Analysis – ITT Population, PCM 301

	VTP N = 206	Active Surveillance N = 207
Number of subjects who initiated a radical treatment, n (%)[a]	12 (5.8)	62 (29.9)
Median time to radical therapy, months (2-sided 95% CI)[c]	NA (NA, NA)	27.0 (26.9, NA)
Subjects who initiated radical therapy at, % (95% CI)[a,b]		
6 months	0.5 (0.1, 3.5)	0.0 (0.0, 0.0)
12 months	1.0 (0.3, 4.0)	4.1 (2.1, 8.0)
18 months	4.7 (2.5, 8.8)	26.5 (20.8, 33.4)
24 months	6.2 (3.6, 10.7)	30.8 (24.8, 38.0)

[a] The percentage of subjects who had radical therapy at each time point is an estimate from Kaplan-Meier analysis and thus differs from the percentage of subjects who initiated radical therapy over the course of the study.
[b] Calculated from the standard Kaplan-Meier curve analysis
[c] p<0.001, from the log-rank test of equality of survival curves across treatment groups

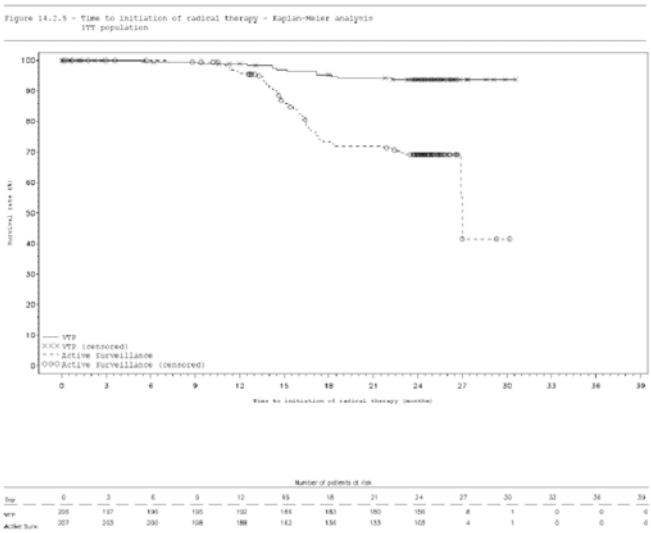


Figure 4 Time to initiation of Radical Therapy by Treatment Group – Kaplan- Meier Analysis – ITT Population PCM301

Tumour burden

Table 30 Tumour Burden at Month 12 and Month 24 by Treatment Group (Local Pathologist Assessment), ITT Population

Characteristic	Month 12		Month 24	
	VTP N = 206	Active Surveillance N = 207	VTP N = 206	Active Surveillance N = 207
Total number of positive cores				
Number of observations	192	186	169	120
Mean[a] (SD)	0.9 (1.32)	2.3 (1.98)	0.6 (1.06)	1.7 (1.59)
Range: minimum, maximum	0, 6	0, 10	0, 5	0, 7
Change from Baseline:				
Mean (SD)	-1.2 (1.42)	0.2 (1.95)	-1.5 (1.23)	-0.3 (1.71)
Range: minimum, maximum	-3, 4	-3, 7	-3, 4	-3, 6
Total cancer core length (mm)				
Number of observations	188	184	168	121
Mean[a] (SD)	2.6 (5.26)	6.8 (9.26)	1.5 (4.05)	5.0 (7.88)
Range: minimum, maximum	0, 33	0, 76	0, 32	0, 46
Change from Baseline:				
Mean (SD)	-1.7 (5.71)	3.0 (9.30)	-2.8 (4.81)	1.3 (7.88)
Range: minimum, maximum	-12, 28	-8, 76	-12, 29	-8, 42
Maximum cancer core length (mm)				
Number of observations	188	184	168	121
Mean[a] (SD)	1.6 (2.74)	3.4 (3.49)	1.0 (2.27)	3.0 (4.06)
Range: minimum, maximum	0, 18	0, 16	0, 14	0, 21
Length categories:				
< 5 mm, n (%)	165 (87.8)	133 (72.3)	156 (92.9)	97 (80.2)
≥ 5 mm, n (%)	23 (12.2)	51 (27.7)	12 (7.1)	24 (19.8)
Change from Baseline:				
Mean (SD)	-1.3 (3.16)	0.8 (3.64)	-1.9 (2.68)	0.4 (4.14)
Range: minimum, maximum	-6, 17	-5, 15	-6, 11	-5, 18

[a]*p*-value< 0.001 from Student *t* test

Severe Prostate-Cancer Related Events

Few subjects experienced a severe prostate cancer-related event (T3 prostate cancer, metastasis or prostate cancer-related death), but only 1 of the subjects who did have such an event (both T3 prostate cancer and metastasis) was in the Tookad Soluble VTP group. At month 24, 11 active surveillance subjects had T3 prostate cancer and 1 had metastases.

Percentage necrosis on Day 7 MRI for Tookad patients

For the first treatment (N=196) mean necrosis was 88.15% (SD 23.99; range 32.2, 161.0). For contralateral treatment (N=62) mean necrosis was 99.76% (SD 32.59; range 18.8, 199.6) and for retreatment (N=11) mean necrosis was 45.86% (SD 18.55, range 10.2, 71.3). Values over 100% represent extension of necrosis to the other lobe. The higher percentage at contralateral treatment reflects the reduction in prostate volume achieved by the first treatment, and the lower percentage at retreatment reflects the difficulty of measurement in the retreated lobe.

The proportion of subjects with extraprostatic necrosis was similar with first and contralateral treatment [147/191 (77%) and 46/62 (74.2%)] respectively and lower at retreatment [5/11 (45.5%)]. Extraprostatic necrosis was of small volume and of no clinical consequence.

PSA

Table 31 Prostate-specific Antigen (ng/mL) by Treatment Group - ITT Population

Time Point	**VTP** **N = 206**	**Active Surveillance** **N = 207**
Baseline, N Mean (SD) Range: minimum, maximum	206 6.19 (2.11) 0.1, 10.0	207 5.91 (2.05) 0.5, 10.0
Month 6, N Mean (SD) Range: minimum, maximum *Change from Baseline* Mean (SD) Range: minimum, maximum	189 3.41 (2.17) 0.2, 12.2 -2.74 (2.30) -8.6, 4.7	193 5.99 (2.47) 0.8, 12.7 0.10 (1.73) -5.6, 5.8
Month 12, N Mean (SD) Range: minimum, maximum *Change from Baseline* Mean (SD) Range: minimum, maximum	185 4.11 (5.05) 0.1, 49.8 -2.08 (5.28) -8.7, 45.5	182 9.67 (19.69) 0.2, 174.0 3.84 (19.83) -9.3, 167.0
Month 24, N Mean (SD) Range: minimum, maximum *Change from Baseline* Mean (SD) Range: minimum, maximum	178 3.07 (2.91) 0.2, 24.6 -3.08 (3.05) -9.4, 14.6	160 5.27 (4.22) 0.2, 19.6 -0.68 (4.10) -9.7, 11.1

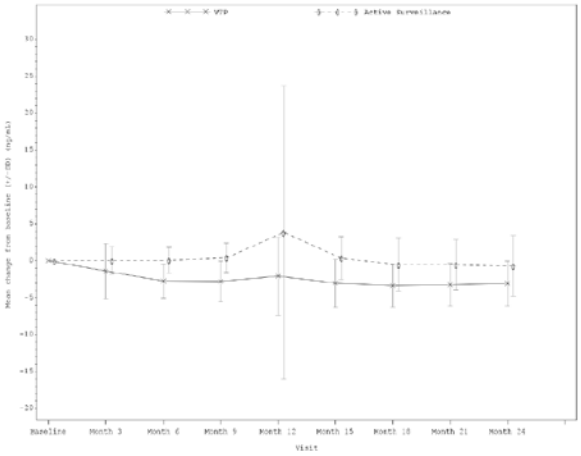


Figure 5 PSA Mean Change from Baseline by Treatment Group – ITT Population

Quality of life

International Prostate Symptoms Score (IPSS)

Subject-reported outcomes showed no statistically significant difference between the Tookad Soluble VTP and the active surveillance group other than a short-term impact on urinary function at Day 7 with Tookad.

The results showed, 7 days after the VTP procedure, on a 35-point scale in comparison to baseline values, a mean increase of 7.2 points (from 7.6 to 14.8) in the ITT population and 7.5 points (from 6.7 to 14.2) in patients meeting the indication criteria. Those results were improved at Month 3 (9.6 in the ITT population and 8.7 in patients meeting the indication criteria) and back to baseline values at Month 6 (7.5 in the ITT population and 6.4 in patients meeting the indication criteria), with further improvement until Month 24 (6.6 in the ITT population and 5.5 in patients meeting the indication criteria). In the Active Surveillance arm, the IPSS score slightly worsened over time until Month 24.

Table 32 PCM301 – Effect on urinary morbidity (IPSS) – ITT population and patients meeting the indication criteria

	ITT population				Patients meeting indication criteria			
	TOOKAD-VTP arm		AS arm		TOOKAD-VTP arm		AS arm	
	n	Mean score (SD)	n	Mean score (SD)	n	Mean score (SD)	n	Mean score (SD)
Baseline	179	7.6 (6.09)	185	6.6 (5.30)	71	6.7 (5.69)	73	6.0 (4.34)
Day 7	180	14.8 (8.64)	Not applicable		72	14.2 (8.89)	Not applicable	
Month 3	179	9.6 (6.86)	190	7.2 (5.75)	71	8.7 (5.72)	72	6.6 (5.11)
Month 6	182	7.5 (6.06)	189	6.8 (5.84)	74	6.4 (5.33)	73	6.3 (5.36)
Month 12	177	7.2 (5.85)	173	7.3 (5.95)	71	5.7 (5.01)	68	7.1 (5.75)
Month 24*	165	6.6 (5.47)	154	8.2 (6.47)	66	5.5 (5.34)	55	8.6 (6.56)

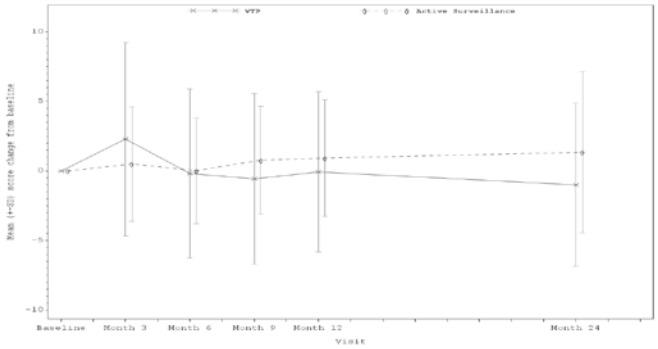
*Scores at Month 24 include patients who underwent radical therapy

Change from Baseline, analysed using an ANCOVA model with treatment group as the fixed effect and Baseline IPSS score as a covariate, also indicated no increase in urinary symptoms with VTP compared to the active surveillance group.

Table 33 International Prostate Symptom Scores and Change from Baseline at Month 24 – Safety Population PCM 301

	VTP N = 197	**Active Surveillance N = 207**
Observed Cases		
Baseline		
Number of observations	179	185
Mean (SD)	7.6 (6.09)	6.6 (5.30)
Month 24		
Number of observations	165	154
Mean (SD)	6.6 (5.47)	8.2 (6.47)
Change from Baseline		
Number of observations	151	138
Mean (SD)	-1.0 (5.86)	1.3 (5.80)
Imputed Cases		
Adjusted change from Baseline		
N[a]	196	204
Mean (SE)	-0.2 (0.35)	1.0 (0.35)
95% 2-sided CI	-0.9, 0.5	0.3, 1.7
Difference in adjusted change from Baseline vs active surveillance		
Mean (SE)	-1.2 (0.50)	
95% 2-sided CI	-2.2, -0.3	
p-value vs active surveillance	0.013	

[a] Number of subjects with non-missing Baseline and Month 24 (imputed) values in the safety population
Sources: Tables 14.3.2.1, 14.3.2.3; Listing 16.4.12.2



[a] potential range of scores: from -35 (best) to + 35 (worst)

Figure 6 IPSS (questions 1-7) – mean change from baseline[a] (and standard deviation) over time (observed cases) – safety population PCM 301

15 question International Index of Erectile Function (IIEF 15) questionnaire

Erectile function domain scores of the 15-question International Index of Erectile Function (IIEF-15) questionnaire showed, 7 days after the VTP procedure, on a 30-point scale in comparison to baseline values, a marked decrease of 7.1 points (from 18.6 to 11.5) in the ITT population and 8.3 points (from 18.4 to 10.1) in patients meeting the indication criteria. There is a subsequent improvement of the erectile function in the following months and, at Month 24, in the VTP arm, the IIEF-15 score was 15.0 in the ITT population and 15.4 in patients meeting the indication criteria.

Table 34 PCM301 – Effect on erectile function (IIEF) – ITT population and patients meeting the indication criteria

	ITT population				Patients meeting indication criteria			
	TOOKAD-VTP arm		AS arm		TOOKAD-VTP arm		AS arm	
	n	Mean score (SD)	n	Mean score (SD)	n	Mean score (SD)	n	Mean score (SD)
Baseline	184	18.6 (10.22)	188	20.6 (9.92)	74	18.4 (10.31)	74	20.8 (10.02)
Day 7	165	11.5 (10.96)	Not applicable		68	10.1 (10.82)	Not applicable	
Month 3	171	14.7 (10.48)	182	21.0 (9.84)	69	14.3 (10.81)	70	21.7 (9.95)
Month 6	176	16.1 (9.98)	185	20.4 (9.83)	68	16.9 (9.78)	72	20.6 (9.85)
Month 12	170	15.1 (10.28)	167	19.9 (10.29)	70	16.7 (10.18)	65	20.4 (10.44)
Month 24*	159	15.0 (10.70)	152	16.8 (11.17)	62	15.4 (11.11)	54	16.4 (11.10)

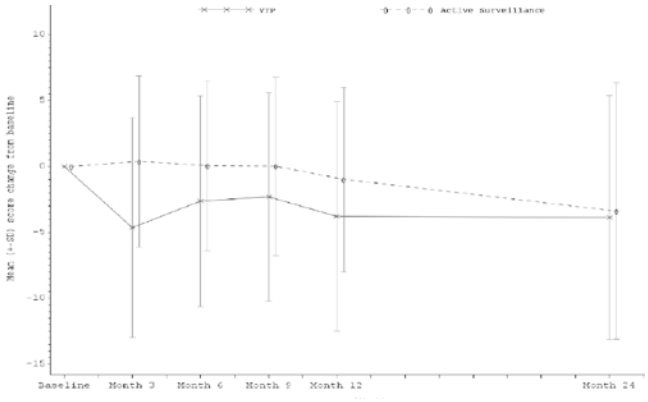
*Scores at Month 24 include patients who underwent radical therapy

Change from Baseline, analysed using an ANCOVA model with treatment group as the fixed effect and baseline erectile function score as a covariate, also indicated no decrease in erectile function with Tookad compared to the active surveillance group.

Table 35 Erectile Function Scores and Change from Baseline at Month 24 - Safety Population PCM 301

	VTP N = 197	Active Surveillance N = 207
Observed Cases		
Baseline		
Number of observations	184	188
Mean (SD)	18.6 (10.22)	20.6 (9.92)
Month 24		
Number of observations	159	152
Mean (SD)	15.0 (10.70)	16.8 (11.17)
Change from Baseline		
Number of observations	150	140
Mean (SD)	-3.9 (9.25)	-3.4 (9.73)
Imputed Cases		
Adjusted change from Baseline		
N[a]	195	203
Mean (SE)	-4.1 (0.57)	-3.1 (0.56)
95% 2-sided CI	-5.2, -2.9	-4.2, -2.0
Difference in adjusted change from Baseline vs active surveillance		
Mean (SE)	-1.0 (0.80)	
95% 2-sided CI	-2.5, 0.6	
p-value vs active surveillance	0.233	

[a] Number of subjects with non-missing Baseline and Month 24 (imputed) values in the safety population
Sources: Tables 14.3.3.1.1, 14.3.3.3.1; Listings 16.4.11.2.1, 16.4.11.2.2.



[a] Potential range of change in scores: from -29 (worst) to +29 (best).

Figure 7 International Index of Erectile Function - Erectile Function Domain - Mean Change from Baseline[a] (and Standard Deviation) Over Time (Observed Cases) – Safety Population

Table 36 EQ-5D Scores and Change from Baseline at Month 24 – Safety Population, PCM 301

	VTP N = 197	**Active Surveillance N = 207**
Baseline		
Number of observations	179	184
Mean (SD)	82.5 (12.31)	81.8 (12.09)
Month 24		
Number of observations	166	150
Mean (SD)	80.9 (14.28)	79.2 (13.25)
Change from Baseline		
Number of observations	151	136
Mean (SD)	-2.5 (12.50)	-2.7 (12.87)
Adjusted change from Baseline		
Mean SE	-2.3 (0.96)	-3.0 (1.02)
95% 2-sided CI	-4.2, -0.4	-5.0, -1.0
Difference in adjusted change from Baseline vs active surveillance		
Mean SE	0.7 (1.40)	
95% 2-sided CI	-2.1, 3.4	
p-value vs active surveillance	0.641	

Ancillary analyses

Co-Primary endpoint A:

The results in the PP population were consistent with the results in the mITT population for Co-primary endpoint A at month 24 and month 12.

Sensitivity analysis (logistic regression) showed no effect of age, number of positive cores, prostate volume and baseline disease status (unilateral/ bilateral) on the outcome (risk ratio in ITT population at 24 months = 3.67 [2.53, 5.33]).

A subgroup analysis by disease status at baseline is presented below.

Table 37 Subgroup analysis of absence of any histology result definitely positive for cancer at 24 months by disease status at baseline - ITT population PCM301

Number of subjects with:	**VTP [N=206] n %**	**Active Surveillance [N=207] n %**
Subgroup: Unilateral	157	163
Observed success Missing biopsy Positive biopsy	77 49.0% 27 17.2% 53 33.8%	23 14.1% 68 41.7% 72 44.2%
Odds-ratio relative to Active Surveillance [95% two-sided CI] Risk ratio relative to Active Surveillance [95% two-sided CI] p-value vs Active Surveillance *	5.86 [3.41; 10.06] 3.48 [2.30; 5.24] <0.001	
Subgroup: Bilateral	49	44
Observed success Missing biopsy Positive biopsy	24 49.0% 11 22.4% 14 28.6%	5 11.4% 18 40.9% 21 47.7%
Odds-ratio relative to Active Surveillance [95% two-sided CI] Risk ratio relative to Active Surveillance [95% two-sided CI] p-value vs Active Surveillance *	7.49 [2.53; 22.19] 4.31 [1.80; 10.32] <0.001	

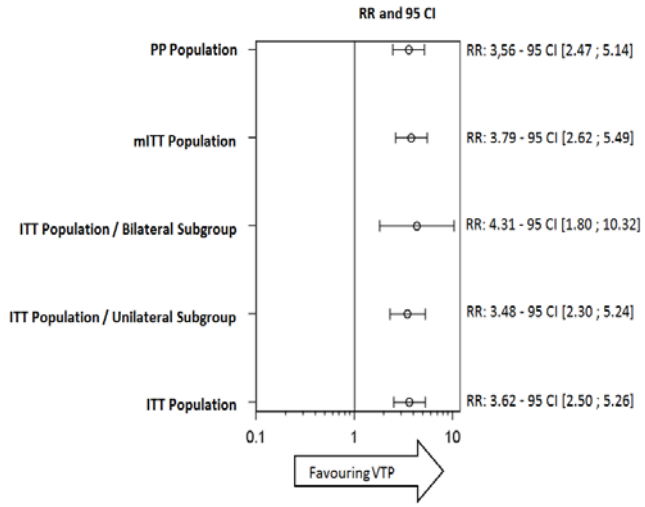


Figure 8 Negative Biopsy Risk Ratios and 95% confidence intervals at month 24, PCM 301

Table 38 Absence of histology result definitely positive for cancer at 12 and 24 months – treated lobe- ITT population PCM 301

Absence of histology results definitely positive for cancer at-	**VTP [N=206] n %**	**Active Surveillance [N=207] n %**
12 months		
Observed success	146 70.9%	54 26.1%
Missing biopsy	14 6.8%	21 10.1%
Positive biopsy	46 22.3%	132 63.8%
Corrected response*	48 23.3%	13 6.3%
24 months		
Observed success	129 62.6%[c]	40 19.3%[c]
Missing biopsy	38 18.4%	86 41.5%
Subjects who had radical therapy leading to missing biopsy	12 5.8%	55 26.6%[a]
Other reasons[b]	26 12.6%	31 15.0%
Positive biopsy		
Corrected response*	39 18.9%	81 39.1%
	28 13.6%	12 5.8%

Subjects with missing biopsies are considered as failures.
Only assessments performed on the treated lobe (or lobe with disease at baseline for active surveillance) are taken into account
* The number of subjects with corrected response corresponds to the subjects considered as failure for the primary analysis due to a result positive for cancer at 12/24 months in the non-treated lobe.

[a]Among the 60 patients who had radical therapy, 5 patients had a Month 24 biopsy

[b]For example: study withdrawal, medical reason, subject refusal

[c] *Risk Ratio (95% CI) = 3.24 (2.41 ; 4.36) ; p value < 0.001*

A post-hoc sensitivity analysis was conducted with respect to missing biopsy results due to radical therapy. All subjects who had undergone radical therapy were counted as subjects with negative biopsy results at Month 24.

Table 39 Absence of any Histology result definitely positive for cancer at Month 24 – Sensitivity Analysis – ITT Population, PCM301

Category of Subjects	**VTP N = 206, n (%)**	**Active Surveillance N = 207, n (%)**
Negative biopsy at Month 24	101 (49.0)	28 (13.5)
Radical therapy leading to missing biopsy by Month 24	12 (5.8)	55 (26.6)
Total counted as negative biopsy for sensitivity analysis	113 (54.9)	83 (40.1)
VTP vs Active Surveillance Risk Ratio (95% CI)	1.37 (1.11, 1.68)	
***p*-value[a]**	0.003	

a From Pearson's chi-square test for observed success

Co-Primary endpoint B:

Sensitivity analysis:

Table 40 Progression by Treatment Group – Cox Proportional Hazards Analysis- and Criteria for Progression - ITT Population

	VTP N = 206 n (%)	Active Surveillance N = 207 n (%)	p-value
Number of subjects progressed at end of follow-up (%)	58 (28.2)	120 (58.0)	<0.001[a]
Crude HR (95% CI)	0.34 (0.25, 0.47)		
Adjusted[b] HR (95% CI) p-value	0.34 (0.24, 0.46) p value ≤ 0.001		
Criteria for progression[c]			
More than 3 cores positive	23 (11.2)	58 (28.0)	< 0.001[d]
Gleason ≥ 4	49 (23.8)	91 (44.0)	< 0.001[d]
Cancer core length > 5 mm	25 (12.1)	51 (24.6)	0.001[d]
PSA > 10 ng/mL in 3 consecutive measures	3 (1.5)	14 (6.8)	0.007[d]
Any T3 prostate cancer	0	4 (1.9)	NA
Metastasis	0	0	NA
Prostate cancer-related death	0	0	NA

[a] From the log-rank test of equality of survival curves across treatment groups
[b] Cox proportional hazards model with treatment as fixed effect and baseline age, number of cores positive, prostate volume and disease status (unilateral/bilateral) as covariates.
[c] A subject might have met > 1 criterion for progression.
[d] From Pearson' s chi-square test
HR = hazard ratio

Analysis of rate of rate of progression and time to progression in the other analysis populations (mITT and PP) showed similar results to the ITT population.

Subgroup analysis of Time to Progression by disease status at baseline is presented below.

Table 41 Subgroup analysis of Time to Progression by disease status at baseline- ITT Population PCM301

	VTP N = 206, n (%)	Active Surveillance N = 207, n (%)
Unilateral	157	163
Number of subjects who progressed	48 (30.6%)	94 (57.7%)
Kaplan-Meier Analysis Median time to progression, months (95% CI)	26.1 (25.2, 30.6)	14.2 (12.9, 23.8)
p-value	< 0.001	
Cox Proportional Hazards Analysis Hazard ratio (95% CI)[a]	0.38 (0.27, 0.54)	
Bilateral	49	44
Number of subjects who progressed	10 (20.4%)	26 (59.1%)
Kaplan-Meier Analysis Median time to progression, months (95% CI)	28.3 (28.3, NA)	14.1 (12.1, 23.9)
p-value	<0.001	
Cox Proportional Hazards Analysis Hazard ratio (95% CI)[a]	0.23 (0.11, 0.48)	

The p-value is from the log-rank test of equality of survival curves across treatment groups
a Cox proportional hazards model with treatment as fixed effect and baseline age, number of cores positive, prostate volume and disease status (unilateral/bilateral) as covariates.

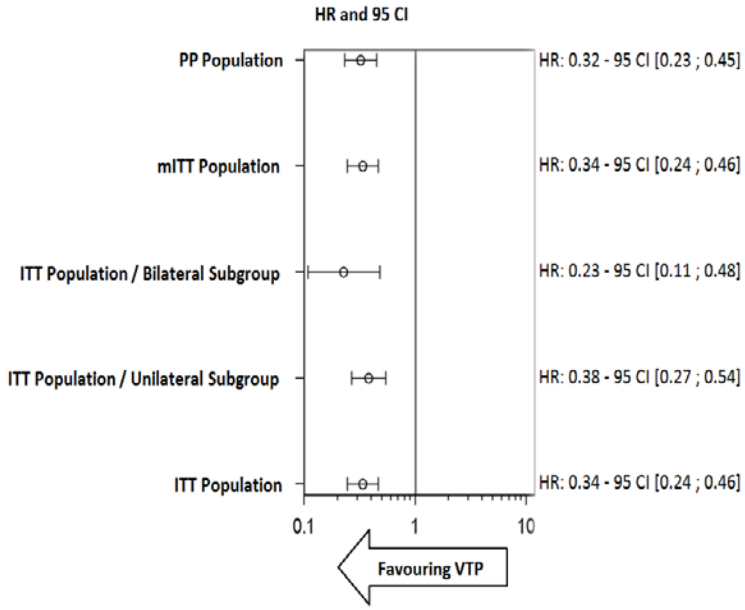


Figure 9 Progression by Treatment Group, Proportional Hazard Ratios and 95% Confidence Intervals – Cox Proportional Hazards Model PCM 301

Table 42 Time to Progression - Sensitivity Analysis (worst case scenario)-ITT Population PCM301

	VTP N = 206, n (%)	**Active Surveillance N = 207, n (%)**
Number of subjects who progressed	74 (35.9%)	143 (69.1%)
Kaplan-Meier Analysis Median time to progression[a], months (95% CI)	26.1 (25.2, 30.6)	13.3 (12.8, 14.7)
p-value[b]	< 0.001	
Cox Proportional Hazards Analysis Hazard ratio (95% CI)[c]	0.38 (0.28, 0.50)	

Patients who withdrew from study or opted for radical prostate treatment before prostate cancer progression are considered as failures.
a Calculated from the standard Kaplan-Meier curve
b From the log-rank test of equality of survival curves across treatment groups
c Cox proportional hazards model with treatment as fixed effect and baseline age, number of cores positive, prostate volume, and disease status (unilateral/bilateral) as covariates.

Table 43 Time to Progression -Treated Lobe- ITT Population PCM301

	VTP N = 206, n (%)	**Active Surveillance N = 207, n (%)**
Number of subjects who progressed	24 (11.7%)	90 (43.5%)
Kaplan-Meier Analysis Median time to progression, months (95% CI)	29.9 (28.3, NA)	23.8 (14.2, 24.4)
p-value	< 0.001	
Cox Proportional Hazards Analysis Hazard ratio (95% CI)[a] P-value	0.17 (0.12, 0.27) p value ≤ 0.001	

The p-value is from the log-rank test of equality of survival curves across treatment groups.
Only assessments performed on the treated lobe (or lobe with disease at baseline for active surveillance) are taken into account
a Cox proportional hazards model with treatment as fixed effect and baseline age, number of cores positive, prostate volume, and disease status (unilateral/bilateral) as covariates.

Kaplan-Meier analysis rate of radical therapy over 48 months

This estimate is based on more points but uses a different outcome (RT rather than progression). The median time to RT is not reached at M48 in the Tookad VTP group, while it is reached at 36.9 months in the Active Surveillance arm.

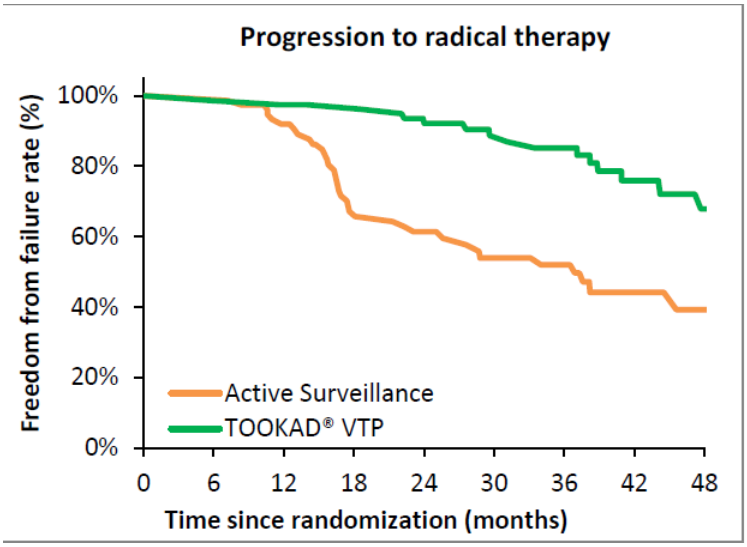


Figure 10 Time to progression to radical therapy – Kaplan-Meier Analysis – Indication population

Treatment post-progression

Details of patients who progressed and treatments received were provided.

Of 58 patients that progressed in the Tookad VTP arm, only 11 underwent radical therapy (5.3%), 18 patients underwent a second VTP procedure and 29 had not received other treatment at the end of the study. Of 121 patients that progressed in the AS arm, 54 underwent radical therapy (26.1%) and 67 had not received any active treatment at the end of the study. Of 121 patients that progressed in the AS arm, 54 underwent radical therapy and 67 had not received any active treatment at the end of the study. Patients in the AS arm were not offered subsequent VTP. In assessing overall tolerability by Month 24, post enrolment patients who underwent a radical therapy were also counted in the scoring of prostate symptoms and erectile function.

Table 44 Progression occurrence and treatments received within 24 months of the PCM301 trial, by treatment arm

	TOOKAD VTP arm N = 206	**AS arm N= 207**
Did not progress	**148 (72%)**	**86 (42%)**
Active treatment#	1 (1%)	8 (9%)
Progressed	**58 (28%)**	**121 (59%)**
Active treatment (% of progressors)	29 (50%)	54 (45%)
• RP	11	46
• BT or RR	-	6
• Cryotherapy	-	2
• HT	-	-
• 2nd VTP	18	-
No Active Treatment at M24	29 (50%)	67 (55%)
RT in extended FU (M48)	10[1]	20[2]

# Includes only radical treatments and excludes sequential VTPs administered as per protocol. Described in individual narratives
RP= Radical Prostatectomy; BT= Brachytherapy; RR= Radical Radiotherapy; HT= Hormonal Treatment; VTP= TOOKAD Vascular Targeted Photodynamic therapy
[1] Rate of 52 p. 100 progressors followed 2 years, considering c. 63% follow-up (FU) at M48
[2] Rate of 45 p. 100 progressors followed 2 years, considering c. 63% FU at M48

The reasons for absence of active treatment in patients who progressed (within 24 months) were provided. The patients who progressed in Study PCM 301 and were not treated were separated into broad categories by the applicant. This included patients who reached the trial endpoint of progression but were considered by the Investigator not to have progressed sufficiently to warrant treatment (Category b).

Table 45 Status of progressing patients (assessed prospectively and retrospectively) not actively treated at M24, by treatment arm

		VTP arm N = 29	AS arm N= 67
a)	M24 Progression only	12 (41%)	19 (28%)
b)	M12 Gleason 6 limited progression [1]	4 (14%) /[24%][2]	21 (31%) /[44%]
c)	M12 Gleason 6 prospectively; retrospectively up-graded to Gleason ≥7 by ORP	9 (31%) /[53%]	18 (27%) /[38%]
d)	M12 Gleason ≥7 prospectively; retrospectively downgraded to Gleason ≤6 by ORP	-	2(3%)/[4%]
e)	M12 Gleason ≥7,both prospective & retrospective readings	4 (14%) /[24%]	7 (10%) /[15%]

[1] >3 positive cores and/or > 5mm core length and/or PSA>10
[2] (Percent figures in parenthesis relate to column total); [percent figures in brackets are relative to M12 biopsy total (excluding "a")]]

Post-hoc analysis without patients ineligible to receive radical treatment

Patients ineligible to receive radical treatment were not counted. A proxy for excluding patients from this analysis was used: 'watchful waiting' (WW) criteria. Usual WW criteria include: life expectancy <10 years and contraindication to radical treatment.

A total of 5 patients were identified who may meet the WW exclusion criteria at any time during the study.

These patients have been removed from the ITT population in a sensitivity analysis of the benefit. This had virtually no observable effect on results. Therefore, the results above and below used the ITT population of the study.

The applicant also provided a post-hoc analysis using an adjusted composite endpoint that includes only the most clinically significant components monitored during the PCM301 study:

- Observation of any Gleason pattern 4 or more (i.e. Gleason Score 7 or more)
- Or any T3 stage prostate cancer
- Or any metastasis
- Or prostate cancer-related death
- Or undergoing radical therapy in absence of progression along one of the criteria above

Table 46 Comparison of Tookad VTP vs. Active Surveillance for hazard ratios of clinically significant progressions over 24 months

Population	AS		AS median time to progression [95% CI]	TOOKAD VTP		VTP median time to progression [95% CI]	Hazard ratio [95% CI]
	N	N event		N	N event		
ITT population	207	111	23.8 [21.7, 24.6]	206	52	28.3 [26.1, NA]	0.36 [0.26-0.51]
EAU AS eligible (≤2 +ve cores)	149	82	23.7 [18.2, 24.8]	146	37	30.6 [26.1, NA]	0.38 [0.26-0.56]
Unilateral disease	158	89	23.7 [17.1, 24.4]	150	41	30.6 [26.1, NA]	0.38 [0.26-0.55]
AS switching to RT when at low risk	21	21	14.4 [13.2, 17.1]	197	50	28.3 [26.1, NA]	0.13 [0.08-0.23]

Additional analyses in the target population

Additional analyses were provided in the target population.

Table 47 Demographic Characteristics by Treatment Group – Target Population

Characteristic	TOOKAD N = 80	Active Surveillance N = 78	Total N = 158
Age (years)[a]			
Mean (SD)	63.9 (6.27)	62.3 (6.32)	63.1 (6.32)
Range: minimum, maximum	48, 74	46, 73	46, 74
Race			
Caucasian, n (%)	78 (97.5)	78 (100)	156 (98.7)
Black, n (%)	1 (1.3)	0	1 (0.6)
Asian, n (%)	0	0	0
Other, n (%)	1 (1.3)	0	1 (0.6)
Body mass index (kg/m^2)			
Mean (SD)	26.05 (3.328)	26.47 (3.360)	26.26 (3.340)
Range: minimum, maximum	18.8, 37.5	19.3, 40.6	18.8, 40.6

Abbreviations: SD = standard deviation; VTP = vascular-targeted photodynamic therapy.

[a] p = 0.126 from Student t test

Table 48 Baseline Disease Characteristics by Treatment Group – Indication Population

Characteristic	TOOKAD N = 80	Active Surveillance N = 78	Total N = 158
Time since diagnosis (months)			
Mean (SD)	4.92 (4.656)	4.81 (4.106)	4.86 (4.380)
Range: minimum, maximum	0.6, 20.3	0.2, 18.9	0.2, 20.3[a]
TNM staging			
T1a, n (%)	0	0	0
T1c, n (%)	66 (82.5)	71 (91.0)	127 (86.7)
T2a, n (%)	14 (17.5)	7 (9.0)	21 (13.3)
PSA (ng/mL)			
Mean (SD)	6.98 (1.796)	7.12 (1.704)	7.05 (1.747)
Range: minimum, maximum	1.0, 10.0	3.1, 10.0	1.0, 10.0
Estimated prostate volume (cc)[b]			
Mean (SD)	37.2 (9.67)	37.6 (9.63)	37.4 (9.62)
Range: minimum, maximum	25, 68	25, 66	25, 68
Unilateral disease, n (%)	80 (100)	78 (100)	158 (100)
Bilateral disease, n (%)	0	0	0
Total number of cores			
Mean (SD)	13.8 (3.64)	14.3 (4.06)	13.0 (3.85)
Range: minimum, maximum	10, 24	10, 26	10, 26
Total number of positive cores[c]			
Mean (SD)	2.2 (0.74)	2.1 (0.76)	2.2 (0.74)
Range: minimum, maximum	1, 3	1, 3	1, 3
1 positive core, n (%)	15 (18.8)	18 (23.1)	33 (20.9)
2 positive cores, n (%)	34 (42.5)	33 (42.3)	67 (42.4)
3 positive cores, n (%)	31 (38.8)	27 (34.6)	58 (36.7)
Total cancer core length (mm)			
Mean (SD)	5.3 (2.64)	3.8 (2.72)	4.5 (2.76)
Range: minimum, maximum	0[d], 14	0[d], 11	0,14

Abbreviations: SD = standard deviation; TNM = tumour, nodes, metastasis; VTP = vascular-targeted photodynamic therapy.

[a] 3 subjects diagnosed for more than 2 years before randomization were removed from the main analysis of the indication population (see Rapporteurs' comments on D120 question 110) – the mean time since diagnosis when including these patients was 5.99 months (SD=7.50).

[b] p = 0.800 from Student t test

[c] p = 0.477 from Student t test

[d] Some of the subjects included on the basis of 2 biopsies at the beginning of the study had 1 of those 2 biopsies negative.

Table 49 Treatment with Tookad – Overall trial and indication populations

Category	Overall trial population N = 206 n (%)	Indication population N = 80 n (%)
Did not receive any treatment	10 (4.9)	1 (1.3)
Received a unilateral treatment before M12	163 (79.1)	79 (98.7)
Received a sequential bilateral treatment before M12	33 (16.0)	0
Received additional VTP treatment after M12	42 (20.4)	22 (27.5)
Received a treatment in previously untreated contralateral lobe after M12	29 (14.1)	17 (21.3)
Received a treatment in previously treated lobe after M12	11 (5.3)	4 (5.0)
Received a treatment in both lobes after M12	2 (1.0)	1 (1.3)
Abbreviations: VTP = vascular-targeted photodynamic therapy.		

Absence of positive biopsy at Month 24

Table 50 Absence of positive histology results at M24 based on lobe diagnosed at baseline – Indication population

Number of Subjects with	TOOKAD N = 80	Active Surveillance N = 78	VTP vs. AS
Negative biopsy in lobe diagnosed at baseline, n (%)	52 (65.0)	11 (14.1)	RR=4.61 (95% CI=2.60-8.16)[b]
Negative biopsy in both lobes, n (%)	36 (45.0)	8 (10.3)	RR=4.39 (95%CI=2.18-8.83)[b]
Positive biopsy in lobe diagnosed at baseline (patients without radical therapy before M24), n (%)	17 (21.3)	33 (42.3)	
Positive biopsy the whole prostate including untreated lobes, n(%)	33 (41.3)	36 (46.2)	
No biopsy result, n(%)	11 (13.8)	34 (43.6)	
No biopsy – Radical Therapy prior to M24, n (%)	6 (7.5)	27 (34.6)	
No biopsy for other reasons[a], n (%)	5 (6.3)	7 (9.0)	

Abbreviations: VTP = vascular-targeted photodynamic therapy; CI = confidence interval.

[a] Study withdrawal, medical reason, subject refusal

[b] p-values<0.001 from Pearson's chi-square test for observed success

The Applicant has conducted a sensitivity analysis where the 22 patients who received a 2nd VTP have been censored. In this analysis, subjects in the Tookad group were 3.99 times (95% CI=2.23-7.13) more likely to have a negative biopsy in the lobe diagnosed at baseline compared to subjects in the Active Surveillance group.

Co-primary endpoint B (difference in rate of treatment failure associated with observed progression of disease from low risk prostate cancer to moderate or higher risk prostate cancer)

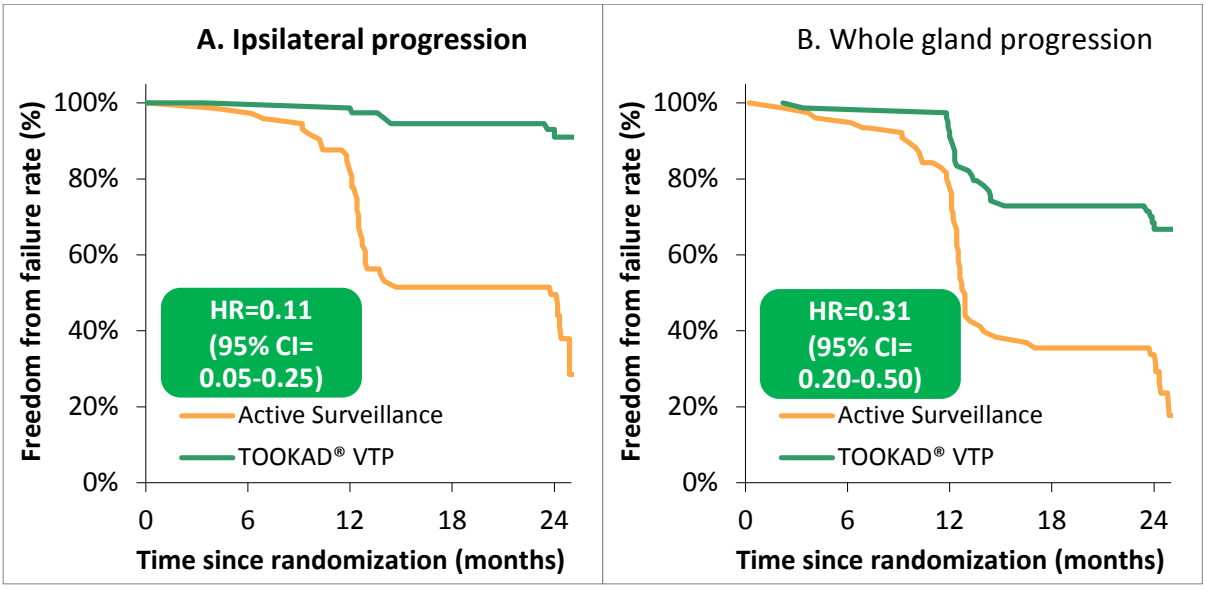


Figure 11 Disease progression – Kaplan-Meier Analysis and Hazard Ratio with Cox regression – Indication population

When considering the ipsilateral progression, the hazard ratio for Tookad vs. Active Surveillance is 0.11 (95% CI=0.05-0.25). When considering whole gland progression, the hazard ratio for Tookad vs. Active Surveillance is 0.31 (95% CI=0.20-0.50).

Table 51 PCM301 – Difference in rate of treatment failure associated with observed progression of disease – Whole prostate gland – ITT population and patients meeting the indication criteria

Number of subjects with	ITT population		Patients meeting indication criteria	
	TOOKAD-VTP arm N = 206	AS arm N = 207	TOOKAD-VTP arm N = 80	AS arm N = 78
Number of subjects progressed at Month 24, n (%)	58 (28.2)[e]	120 (58.0)[e]	27 (33.8)[f]	53 (67.9)[f]
Progression to Gleason ≥ 4	49 (23.8)	91 (44.0)	19 (23.8)	40 (51.3)
[e]Adjusted Hazard Ratio (95% CI) = 0.34 (0.24 ; 0.46) ; p value ⩽ 0.001 [f]Adjusted Hazard Ratio (95% CI) = 0.31 (0.20 ; 0.50) ; p value ⩽ 0.001				

Table 52 Disease progression – Summary of Hazard Ratios with Cox regression in the different populations of interest

Population	**Ipsilateral progression Hazard Ratio (95% CI)**	**Whole gland progression Hazard Ratio (95% CI)**
Over trial	0.17 (0.12-0.27)	0.34 (0.24-0.46)
Indication	0.11 (0.05-0.25)	0.31 (0.20-0.50)
Indication with censoring of 2nd VTP	0.10 (0.04-0.24)	0.32 (0.20-0.51)

Results in treated lobe/lobe with disease at baseline

Table 53 PCM301 – Co-primary efficacy endpoints – Treated lobe / lobe with disease at baseline – ITT population and patients meeting the indication criteria

Number of subjects with	ITT population		Patients meeting indication criteria	
	TOOKAD-VTP arm N = 206	AS arm N = 207	TOOKAD-VTP arm N = 80	AS arm N = 78
A: Rate of absence of definite cancer based on histology at 24 months				
Negative biopsy, n (%)	129 (62.6)[a]	40 (19.3)[a]	52 (65.0)[d]	11 (14.1)[d]
No biopsy result, n (%)	38 (18.4)	86 (41.5)	11 (13.8)	34 (43.6)
Subjects who had radical therapy leading to missing biopsy, n (%)	12 (5.8)	55 (26.6)[b]	6 (7.5)	27 (34.6)
Other reasons[c], n (%)	26 (12.6)	31 (15.0)	5 (6.3)	7 (9.0)
Positive biopsy, n (%)	39 (18.9)	81 (39.1)	17 (21.3)	33 (42.3)
[a]Risk Ratio (95% CI) = 3.24 (2.41 ; 4.36) ; p value < 0.001 [b]Among the 60 patients who had radical therapy, 5 patients had a Month 24 biopsy [c]For example: study withdrawal, medical reason, subject refusal [d]Risk Ratio (95% CI) = 4.61 (2.60 ; 8.16) ; p value < 0.001				
B: Difference in rate of treatment failure associated with observed progression of disease				
Number of subjects progressed at end of follow-up, n (%)	24 (11.7)[e]	90 (43.5)[e]	7 (8.8)[f]	39 (50.0)[f]
[e]Adjusted Hazard Ratio (95% CI) = 0.17 (0.12 ; 0.27) ; p value ≤ 0.001 [f]Adjusted Hazard Ratio (95% CI) = 0.11 (0.05 ; 0.25) ; p value ≤ 0.001				

Treatment post progression

Table 54 PCM301 – Number of subjects with radical treatment at 24 months – ITT population and patients meeting the indication criteria

Characteristic	ITT population		Patients meeting indication criteria	
	TOOKAD-VTP arm N = 206	AS arm N = 207	TOOKAD-VTP arm N = 80	AS arm N = 78
Number of subjects who initiated a radical treatment, n (%)	12 (5.8)	62 (29.9)	6 (7.5)	28 (35.9)
Number of subjects who initiated a radical treatment after progression, n (%)	11 (5.3)	54 (26.1)	5 (6.3)	25 (32.1)

Absence of disease progression at M15 and M27 in the target population

The proportions of absence of disease progression in the initially diagnosed lobe and the whole gland at M15 and M27 were evaluated. These time points have been used to ensure all progressions were taken into account in both arms for each of the biopsy timeframes.

Table 55 Absence of disease progression at M15 and M27 in initially diagnosed lobe – Indication sub-population

	Absence of progression at M15		**Absence of progression at M27**	
Subjects with	**TOOKAD VTP**	**Active Surveillance**	**TOOKAD VTP**	**Active Surveillance**
Available biopsy or progression at prior biopsy, n	79	73	71	67
Absence of disease progression, n (%)	75 (95)	40 (55)	64 (90)	28 (42)

Table 56 Absence of disease progression at M15 and M27 in whole gland – Indication sub-population

	Absence of progression at M15		**Absence of progression at M27**	
Subjects with	**TOOKAD VTP**	**Active Surveillance N=73**	**TOOKAD VTP N=71**	**Active Surveillance N=67**
Available biopsy or progression at prior biopsy, n	79	73	76	71

	Absence of progression at M15		Absence of progression at M27	
Subjects with	**TOOKAD VTP**	**Active Surveillance N=73**	**TOOKAD VTP N=71**	**Active Surveillance N=67**
Absence of disease progression, n (%)	58 (73)	26 (36)	49 (64)	18 (25)

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 57 Summary of efficacy results of study CLIN1001 PCM301

Title: A European Randomised Phase 3 Study to Assess the Efficacy and Safety of TOOKAD Soluble for Localised Prostate Cancer Compared to Active Surveillance			
Study identifier	CLIN1001 PCM301 (EUDRACT#: 2010-021900-93)		
Design	Randomized, open-label, multicenter, Phase 3 Study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		08 March 2011 to 25 June 2015 not applicable Post-study 5-year follow up ongoing
Hypothesis	Superiority		
Treatments groups	TOOKAD VTP		TOOKAD VTP, one procedure, number randomized 206
	Active surveillance		No treatment. 24 months active surveillance, number randomized 207
	Co-Primary endpoint	B	rate of treatment failure (progression from low-risk to moderate or higher-risk prostate cancer)
	Secondary endpoints		- the total cancer burden in the prostate - the rate of additional prostate cancer radical therapy - the rate of severe prostate cancer-related events: cancer extension to T3, metastasis, and prostate cancer-related death - the rate of adverse events (AEs) - the rate of incontinence, erectile dysfunction, and urinary symptoms The overall quality of life was recorded for potential utility and descriptive studies.
Database lock	21 August 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) Time points: 24 months		
Descriptive statistics and estimate variability	Treatment group	VTP	Active Surveillance
	Number of subject - ITT	206	207
	Median time to progression (Kaplan-Meier)	28.3	14.1
	(95% CI)	(26.0, 30.6)	(12.9, 23.8)
	Progression by treatment group (Cox Proportional Hazard Analysis)	58 (28.2%)	120 (58.0%)
	Adjusted* HR (95% CI)	0.34 (0.24, 0.46)	
	Rate of absence of definite cancer (Pearson chi-square) Month 24	49%	13,5%
	Risk Ratio (95%CI) Odds Ratio (95%CI)	3.62 (2.50, 5.26) p <0.001 6.15 (3.79, 9.97) p <0.001	
Effect estimate per comparison	Co-Primary endpoint Treatment Failure (B)	Comparison groups	VTP vs. active surveillance
		Log-rank	28.3 vs. 14.1 months
		(CI 95%)	(26.8;30.6),(12.9;23.8)
		P-value	< 0.001
	Co-Primary endpoint Absence of definite cancer (A)	Comparison groups	VTP vs. active surveillance
		Pearson chi-square	Month 24
		Risk Ratio Odds Ratio	3.62 (2.50, 5.26) 6.15 (3.79, 9.97)
		P-value	< 0.001
	Secondary endpoint	Comparison groups	VTP vs. active surveillance

	Time to initiation of radical therapy	Kaplan-Meier Log-rank	6.2 vs. 30.8 %
		95% CI	(3.6;10.7) (24.8;38.0)
		P-value	< 0.001
Analysis description	**Co-primary Analysis** The Hochberg procedure was used to adjust for multiplicity of the 2 co-primary endpoints. Adjusted analyses for both co-primary endpoints were also conducted.		

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	91/196 (46.4%)	7/196 (3.6 %)	1/196 (0.5%)
Non Controlled Trials	85/275 (30.9 %)	9/275 (3.3 %)	0/275 (0 %)

Supportive study(ies)

Study PCM304

Study Title: "Study of the Efficacy, Safety and Quality of Life after Tookad Vascular Targeted Photodynamic therapy (VTP) for Minimally Invasive Treatment of Localized Prostate Cancer".

This is a completed, multi-centre, confirmatory Phase 3, open label trial conducted in three Latin American countries (Mexico, Peru and Panama).

Primary objective: confirm that a significant proportion of patients will be prostate cancer-free on the Month 12 biopsy. The primary efficacy endpoint was the proportion of patients with a negative prostate biopsy at Month 12.

Of the 81 patients enrolled in this study, three were anesthetised but did not receive the first VTP procedure because they were found to have had a previous trans-urethral resection (TURP) of the prostate. A total of 78 patients were treated with 4 mg/kg Tookad and 200 J/cm laser light. 76 received the first VTP procedure according to protocol, and in two cases power cuts during the procedure resulted in delays of approximately 10 minutes between WST11 injection and laser illumination. Seventeen patients, who had bilateral disease at baseline, underwent a second VTP procedure in order to treat contralateral disease before Month 6 (and in one case after Month 6).

Eight patients who had a positive Month 6 biopsy received an additional treatment (three patients in the previously treated lobe and one patient in the contralateral lobe and four patients had retreatment in a previously treated lobe as well as treatment to previously untreated contralateral lobes.

Prostate biopsies were made between 321 days and 479 days after the inclusion visit, with a median of 375 days.

Among the 71 patients who had Month 12 biopsies results available, 60 (84.5%) patients had a negative biopsy and 11 (15.5%) patients had a positive biopsy; among the latter patients, nine had a positive biopsy

in the treated lobe, and two in the contralateral, untreated lobe. The percentage of negative biopsies was consequently 74.1% (60/81) in the ITT population (95% CI: [63.1%; 83.2%]).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The submission is based on a randomized phase III trial to assess the efficacy and safety of Tookad VPT for Localised Prostate Cancer *versus* active surveillance in localised prostate cancer (PCM 301) compared to Active Surveillance.

The design of the single pivotal Phase 3 study in support of the Tookad application is generally in accordance with the key points of Appendix 4 to the Guideline on the Evaluation of Anticancer Medicinal Products in man (EMA/CHMP/703715/2012 Rev.1) and the scientific advice received. The duration of follow-up of 2 years and the proposed extended study (Study CLIN1001 PCM301 FU5) was accepted although the CHMP commented that prolonged follow-up of these patients to assess clinical outcome, in particular overall survival, should be implemented.

In the active surveillance arm, the recruited population underwent active surveillance once the study commenced. Baseline PSA values were provided but no description of PSA velocity. The mean time from diagnosis was about 6 months and standard deviation indicated that most patients were diagnosed within the previous 12 – 14 months but some patients were diagnosed over 4 years prior to trial entry. Hence, there appeared to be population heterogeneity, from relatively newly diagnosed patients where the PSA velocity and appropriateness of active surveillance was still being established, to patients in whom low risk prostate cancer has been stably present over a number of years. It was shown that delay between diagnosis and randomization dates was evenly distributed across the two arms and that the treatment difference between arms was maintained when counting progression from diagnosis instead of from randomization. A re-analysis of the progression co-primary endpoint B was performed on the subpopulation of patients with more than 6 months from diagnosis vs. patients with less than 6 months from diagnosis. The reduction of progression in the Tookad VTP vs. AS was significant in both groups tested. The difference was not statistically significant between these groups.

Active surveillance is offered to men with low risk prostate cancer for whom radical prostatectomy or radical radiotherapy is suitable. The protocol stipulated a life expectancy of 10 years but this was left to the discretion of the investigators and patients up to the age of 85 years were included. The mean age and the median age of the patients in the trial were relatively low considering the diagnosis of prostate cancer, but might represent a PSA testing bias, as early prostate cancer is usually suspected from PSA and presents itself without symptoms. Results in patients less than 75 years of age were similar to the full study population for both co-primary endpoints.

Progression free survival in low risk prostate cancer is expected to be long. Therefore the applicant used surrogate markers in the clinical assessment of efficacy, namely MRI findings, biopsy results and PSA in all of the clinical studies which is considered acceptable.

There were 39 major deviations in the VTP and 26 in the active surveillance group. It is inevitable in an open label study that there will be more protocol deviations in the group receiving treatment. 11 patients with bilateral disease were treated in only 1 lobe. This was justified by the applicant as being consistent with the intention of focal treatment by treating the lobe with the highest tumour burden. Retreatment of the same lobe or sequential treatment of the contralateral lobe of the prostate are not recommended (see sections 4.2 and 4.4). The decision to modify the treatment administered illustrates the importance of operator experience in treatment planning.

Attempts were made to make the treatment implementation and outcome evaluation uniform and robust. The CTGC compared the MRI and the final ultrasound based treatment plans for the first cases at each centre (as needed) and verified post-hoc 10% of randomly selected cases to ensure consistency. An independent, blinded Outcomes Review Panel (ORP) of experts (urologist, pathologist and statistician) reviewed the pathology reports. The Month 12 and 24 biopsies were read by one central uro-pathologist, blinded to the treatment assignment and to the local pathologist reading, and all discrepant cases were adjudicated by the ORP pathologist. Although blinded, it is presumed that it would be possible to determine on analysis of the prostate biopsies who has received VTP.

Baseline characteristics of the two arms are well balanced and comply with the inclusion criteria. 11 patients were excluded because their prostate was not in the range 25-70cc.

Efficacy data and additional analyses

Tookad produced a statistically significant improvement in a patient's probability of a negative biopsy at 24 months after treatment (49% vs. 13.5%, RR=3.62) (Co-Primary endpoint A). Results were similar in the mITT and PP populations. A total of 124 patients (30%) lacked a month 24 biopsy. This was mainly driven by patients undergoing radical therapy particularly in the active surveillance arm. The number for whom a biopsy was expected but not performed was equivalent in the 2 groups (n=26, 12.6%). In all analyses, subjects with missing biopsies were considered failures. This is an appropriate assumption but favours the Tookad arm; 41.5% of biopsies were missing at Month 24 in the active surveillance arm.

Sensitivity analysis (logistic regression) showed no effect of age, number of positive cores, prostate volume and baseline disease status (unilateral/ bilateral) on the outcome (risk ratio in ITT population at 24 months = 3.67 [2.53, 5.33]). Results were similar on subgroup analysis of unilateral (RR 3.48 [2.30, 5.24]) and bilateral (4.31 [1.80, 10.32]) disease; in both groups 49% of VTP patients had no histological evidence of cancer on 24 month biopsy.

Co-primary endpoint A looked at biopsy results in both lobes, regardless of disease status at baseline and whether the lobe was treated. The additional analysis looking at results in the treated lobe was more reassuring with regards to the proportion of patients with negative biopsies at 24 months (62.6%) vs 19.3% in the Tookad and AS arm respectively. Results showed the known lack of sensitivity of TRUS-guided biopsy (28/ 207, 13.5% subjects on active surveillance had a negative biopsy at Month 24). Biopsies cannot sample the whole area and will not obtain tissue near the capsule, the likely site of residual disease post Tookad – VTP.

A post-hoc sensitivity analysis that assumed missing biopsies due to radical therapy to be negative, still favoured Tookad, although the effect size was smaller (54.9% vs. 40.1%, RR 1.37 [1.11, 1.68] p=0.003). The month 24 biopsy was not performed in about 11% of patients, not previously classified as treatment failures. However, sufficient data were available for subjects in the VTP group to calculate the failure rate.

At 12 months 45.6% of ITT patients in the Tookad group had a positive biopsy, half of which were due to as yet untreated known disease at baseline. Separate algorithms and cut-offs of PSA elevation are used post prostatectomy and post radical radiotherapy to indicate a need to further therapy. Neither of these applies post Tookad VTP when a prostate lobe remains unaffected by treatment. Separately there is established guidance on active surveillance follow-up. Therefore, a follow-up regimen was proposed after Tookad VTP, based on the protocols for the PCM301 study and its follow-up study, along with common AS follow-up strategies. Following Tookad VTP, patients should undergo digital rectal examination (DRE) and have their serum PSA monitored, including an assessment of PSA dynamics (PSA doubling time and PSA velocity). PSA should be tested every 3 months for first 2 years post VTP and every 6-month thereafter in order to assess PSA dynamics (PSA Doubling Time (DT), PSA velocity). Digital Rectal Examination (DRE) is recommended to be performed at least once a year and more often if clinically justified. Routine biopsy is recommended at 2-4 years and 7 years post VTP, with additional biopsies based on clinical/ PSA assessment. mpMRI may be used to improve the decision making but not, at present, to replace biopsy.

In case of positive biopsies, patients who exceed the threshold for low risk disease (i.e. have GS >6, >3 positive cores or any single core length >5mm) should receive a treatment recommendation for radical therapy.

There is insufficient evidence to advocate a second VTP at present as an alternative to AS or radical therapy. The follow-up strategy is acceptable.

With regards to Co-primary endpoint B, the proportion of subjects who progressed over 24 months in the Tookad group was lower than in the active surveillance group (28.2% vs. 58.5%; HR=0.34 [0.25; 0.47]). No significant effect of covariates [baseline age, number of cores positive, prostate volume and disease status (unilateral/bilateral)] was observed; crude and adjusted HRs was similar. Looking at the individual criteria for progression, each parameter was reduced by Tookad.

The results appeared robust to different analyses (mITT and PP populations), baseline disease status (uni/ bilateral) and the sensitivity analysis that assumed that all patients who withdrew or opted for radical therapy were treatment failures (progression 35.9% vs 69.1%; HR = 0.38 [0.28, 0.50]). The Median time to progression was twice as long in the Tookad as the active surveillance group (28.3 vs. 14.1 months, $p<0.001$). The 95% CIs (26.0, 30.6) were fairly tight in the Tookad group, suggesting a consistent 2 – 2 ½ years until progression. The largest proportion of patients on active surveillance that progressed did so in the first 12 months. Baseline biopsies were taken at different time points up to 12 months from study inclusion and a sensitivity analysis was presented for both arms of time to progression from prostate biopsy rather than randomisation. The estimated time to progression was longer in both arms by approximately 3 months when taken from the biopsy date (AS vs. VTP 17 vs 32 months) rather than the date of randomisation (14.1 vs. 28.3 months).

When progression in the treated lobe only was assessed, the number with progression in both groups decreased, but this was more marked in the VTP group. The median time to progression increased in the active surveillance arm from 14.1 to 23.8 months.

The duration of biopsy follow-up in the trial was insufficient to accurately determine TTP. It is also noted that this is histological rather than biochemical progression as reported for other treatment modalities and the correlation between these two measures is unclear.

When using the 48-month follow-up information from the extension study for the right censorship, the median-time to progression is not reached at 30 months in the Tookad arm vs 36.9 months (data not shown). The applicant estimated time to progression using parametric survival analysis, which gave an estimate in the region where there is no data. The PSA cut off >10 is less informative in the VTP arm as patients started with a lower absolute PSA post Tookad (3 patients in the VTP vs 14 in the AS arm progressed on the PSA endpoint). Overall, there was no reliable way to detect progression and the need for radical therapy in the Tookad arm after 2 years. The numbers of patients undergoing active/ radical therapy is similar in both arms from 24 months onwards, but the results are dominated by the excess of radical therapy in the AS arm during the first 2 years. Therefore, the delay to progression analyses as well as the risk of/time to receiving radical therapy analysis should be considered with caution.

Absence of disease progression at M15 and M27 in the target population was also reported. The proportions of patients with no disease progression in the initially treated lobe were substantially higher in the Tookad than in Active Surveillance arm, with 95% vs. 55% of patients without ipsilateral disease progression at M15 respectively and 90% vs. 42% at M27. Hence, the difference between the two arms at M15 was 40% and increased to 48% at M27. When considering the whole gland, the proportions for absence of progression were lower with 73% and 36% at M15 for Tookad and Active Surveillance respectively and 64% and 25% at M27. The difference between the two arms at M15 was 37%, which is comparable to the one observed for ipsilateral progression only. The difference increased minimally at M27 (39%) and was somewhat lower than the one observed for ipsilateral progression only. Overall, this analysis confirms the significant reduction in progression of disease and need for radical therapy, which had been reported previously based on the review of hazard ratios in Kaplan-Meier analyses.

Medium and long term outcomes following subsequent radical therapy (surgery or radiotherapy) have not been followed up, specifically any impact of prior Tookad VTP on oncological parameters post-surgery (T stage, Gleason score, positive margins), undesirable genitourinary effects, radiotherapy toxicity and ultimately survival (see also discussion on clinical pharmacology and clinical safety). To compensate for the relatively short follow-up for progression, patients can enter into a long-term follow-up programme for a further 5 years (Study CLIN1001 PCM301 FU5). In this extension study, follow-up will be done through periodical data collection that will inform the evolution of the prostate cancer, complications and treatments as well as quality of life. This will also include an in-depth biopsy study to measure cancer progression in patients who were enrolled (see Annex II and RMP) and is expected to provide reliable data on progression after 24 month.

Together with the PAES CLIN1501 PCM401 (see discussion on clinical pharmacology), the long term follow up of study PCM301 will provide relevant long term efficacy data on Tookad and is therefore included as a condition in Annex II of the opinion. The protocol for PAES CLIN1501 PCM401 and the SAP of the follow-up study PCM301 FU5 (PAES) will discriminate the use of other prostate cancer therapy as radical treatment (radical prostatectomy, prostatic radiotherapy, low dose rate brachytherapy, high dose rate brachytherapy); other active treatment (cryotherapy, ultrasound therapy, further VTP); palliative therapy (hormonal therapy, chemotherapy, palliative radiotherapy (location -pelvis, bone, other), TURP, other non-radical therapy). Updates on the status of recruitment are expected to be given by the applicant post-authorisation.

Criteria for retreatment of the same lobe were not presented but were presumed to be the same as for initial treatment. It is not known how many patients were considered eligible for or were offered retreatment. Very few patients actually underwent retreatment. The percentage necrosis was higher with initial (88.15%) and contralateral (99.76%) treatment than retreatment (45.86%). This was attributed to difficulty of measurement in the retreated lobe. Extraprostatic necrosis was less at retreatment (45.5%) vs. 77% and 74.2%, suggesting an element of investigator concern regarding dose.

Overall, insufficient patients underwent retreatment of the ipsilateral lobe or sequential treatment of the contralateral lobe to determine the efficacy and safety of a second Tookad VTP procedure (see SmPC section 4.4). Furthermore, simultaneous treatment of both prostate lobes was associated with an inferior outcome in clinical trials and should not be performed (data not shown). Therefore, retreatment of the same lobe or sequential treatment of the contralateral lobe of the prostate are not recommended (see sections 4.2 and 4.4).

With regards to the secondary endpoints, Tookad Soluble VTP clinically and statistically ($p < 0.001$) significantly increased the time to initiation of radical therapy; 12 (5.8%) subjects in the Tookad VTP group underwent radical therapy compared to 60 (29.0%) in the active surveillance group within the 2 years of the study. In the Tookad VTP group 1 subject and in the active surveillance group 8 subjects underwent radical therapy without meeting the co – primary endpoint B definition for progression.

Only 60/121 active surveillance and 12/58 Tookad patients who progressed underwent radical therapy. The absence of active treatment (radical therapy or 2nd VTP) after progression in both arms is high compared to published series e.g. in the PRIAS study (Bul 2013) of active surveillance for low risk prostate cancer in 2494 men, 93.3% (387/415) patients that experienced protocol defined progression underwent treatment, either prostatectomy or radiotherapy. The reasons for absence of active treatment after progression (within 24 months) were provided (see table 48). The patients who progressed in Study PCM 301 and were not treated were separated into broad categories by the applicant. This included patients who reached the trial endpoint of progression but were considered by the investigator not to have progressed sufficiently to warrant treatment (Category b). Interestingly this appears to be in favour of the VTP arm; 24% in the VTP vs. 44% of patients in the AS arm were deemed to have progressed (and therefore contributed to Co-primary endpoint B) but progression was too limited to warrant treatment. However, the numbers involved are too small to draw any conclusions.

Five patients that were clearly ineligible for active surveillance/ radical therapy were highlighted. In order to confirm patient eligibility to RT, the Applicant reviewed the medical history of all patients. All remaining 408 patients were eligible for radical therapy on reported clinical grounds. Of note, among these, 10 patients were over 75 years old (5 patients in each arm). The Life expectancy at 75 is 10 years on average in the European countries where the study was conducted. However, its assessment remains patient specific if there is no age limit set in advance. A sensitivity analyses was done considering a worst case scenario, excluding the 5 patients with disputable RT eligibility and the 10 patients aged >75 years. This had also no meaningful impact on efficacy and benefit results (data not shown).

The post-Baseline mean PSA values in the Tookad group were lower than the mean values at the corresponding time points in the active surveillance group and the Tookad D baseline value. The main point of the PSA assay in the Phase III trial was to verify that the PSA levels at the different time points according to the procedure remained below the baseline PSA levels. Variability in PSA can be difficult to evaluate and correlate with disease progression, especially as there is normal prostate tissue remaining. Although there are doubts regarding the use of PSA threshold >10, that could be biased towards Tookad as patients who underwent VTP were starting with a lower absolute PSA level, within the 24 months of study PCM301 just 4 patients (3.3%) in the AR arm and 1 patient (1.7%) in the Tookad arm had PSA progression alone as criterion for progression.

Co-primary endpoint A and B were presented by PSA density (presumed to be baseline PSA density) (data not shown). Individuals with a higher PSA density (>0.2) appeared to derive less benefit in terms of time to progression (co-primary endpoint B) than those with a lower PSA density regardless of treatment group. PSA density did not influence the chance of a negative biopsy. Furthermore, the proportion of patients that achieved co-primary endpoint A (absence of positive biopsy) in the VTP compared to the AS arm at 12 and 24 months did not appear related to PSA velocity. Co-primary endpoint B was not presented by PSA velocity.

QoL data (EQ5D) was presented for Baseline and Month 24 only. IPSS scores in the Tookad group increased at Month 3 but were equal or less than baseline from month 6 onwards. The mean IPSS score in the active surveillance group increased marginally over the study period and were higher than in the Tookad group at Month 24. The mean IPPS showed a marked increase in the VTP arm at day 7 post VTP procedure; it nearly doubled from 7.6 to 14.8 on a 35 point scale. IPSS then improved and returned to baseline by Month 6. IIEF-15 scores showed moderate worsening in erectile function up to 3 months after the procedure, but the result at Month 24 was comparable in the 2 groups. Erectile dysfunction deteriorated at Day 7 and, although it improved after this time point, it never regained baseline levels. The SmPC adequately reflects that erectile dysfunction may occur even if radical prostatectomy is avoided. Some degree of erectile dysfunction is possible soon after the procedure and may last for more than 6 months (see section 4.8).

The applicant presented the various facets of the patient reported outcomes for the active surveillance arm split by whether the patient remained on active surveillance or underwent radical therapy (data not shown). There was no difference in quality of life (QoL) reflected by the EQ5D between those that underwent radical treatment (RP) and those that remained on active surveillance. This is in line with QoL at Month 24 that was not influenced by Tookad treatment. However, the applicant states that the QoL criteria evaluated by the EQ5D questionnaire are not known to be impacted by radical treatment for prostate cancer. Therefore, it is not clear why the questionnaire was originally chosen for use in the study. With regards to the IPSS score those that underwent RP had consistently better scores than those that did not. This could be due to chance or the fact that patients with better scores were selected for radical therapy. It is difficult to compare these scores with the scores post Tookad VTP as most radical therapy was undertaken after 12 months so the only follow up available was at 24 months. However, by this time point any decline in IPSS had resolved; there was no difference between patients that underwent radical therapy, persisted with active surveillance or underwent Tookad VTP. Erectile function score was similar between the AS alone and RP groups up to 12 months. After this time point most radical therapy occurred. At 24 months erectile function was similar in the AS alone group to baseline. This is important as it suggests that there is no ‘natural’ decline in erectile function in those that don’t undergo radical therapy. This was not evident from the full AS population. There was a marked decline from 12 to 24 months in those that underwent RP. The mean score at 24 months for erectile function in those that underwent RP was 12.1, a decrease from Baseline of -9.3. It is difficult to compare this to the score post VTP, although the 12 month score post VTP (mean 15.1) may be the most relevant.

Further to the SAG oncology consultation (see below) which suggested that Tookad VTP could be a useful procedure for higher risk patients (in this low risk group) who prefer deferring radical therapy and potentially avoiding it altogether, the applicant proposed a revised indication in patients with a life expectancy≥ 10 years and who meet the following criteria: previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with: Clinical stage T1c or T2a; Gleason Score ≤ 6, based on high-resolution biopsy strategies; PSA ≤ 10 ng/mL; 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1 - 2 positive cancer cores with ≥ 50 % cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/cm^3.

The population targeted by the indication represents 38% of the overall trial population with a good balance of the Tookad arm (80 patients, 39% of overall trial population) and the Active Surveillance arm (78 patients, 38% of overall trial population). Overall, the differences highlighted in the targeted population in comparison to the overall trial population are consistent with the exclusion of a very low risk population.

Co-primary endpoint A (rate of absence of definite cancer i.e. absence of positive histology) favoured the Tookad arm. Tookad produced statistically significant improvement in the patients' probability of a negative biopsy result at 24 months after treatment. In the targeted population, 65.0% of subjects in the Tookad group had a negative biopsy in the lobe diagnosed at baseline compared to 14.1% of subjects in the Active Surveillance group. Hence subjects in the Tookad group were 4.61 times more likely to have a negative biopsy in the lobe diagnosed at baseline compared to subjects in the Active Surveillance group. The difference between the two treatment groups is greater in the targeted population than the overall trial population, where this figure was 3.24.

Based on the sensitivity analysis where the 22 patients who received a 2nd VTP have been censored, the impact of the 2nd VTP on the results of co-primary endpoint appears to be moderate, especially when focusing on the initially diagnosed lobe.

Co-primary endpoint B (difference in rate of treatment failure associated with observed progression of disease from low risk prostate cancer to moderate or higher risk prostate cancer) favoured the Tookad arm.

Overall, the analyses showed that trial results were better for the key endpoints used for the comparison of Tookad vs. Active Surveillance.

Based on data available to date, the restricted use of Tookad in the target indication sub-population (unilateral low-risk, excluding very low-risk disease), with limitation to a single procedure enables to maximize the positive benefits of the treatment, while minimizing the risk of compromising salvage radical therapy. Although still preliminary and somewhat uncertain, the longer-term data available to date points to maintenance of the benefits with no signal of increased risk. To further investigate long-term efficacy of Tookad and its impact on disease progression including potential impact on the efficacy of subsequent radical therapy in patients with low risk prostate cancer as well as further characterise the long term safety of Tookad, the results of two PAES, study CLIN1001 PCM301 FU5 and study CLIN1501 PCM401, will be provided post-authorisation (see Annex II).

Additional expert consultation

The SAG Oncology was asked to provide their view on the following issues:

Tookad VTP is claimed to primarily defer rather than avoid the need for radical therapy (median time to progression, defined largely by criteria for radical therapy, 28.3 months). The main adverse effects of Tookad VTP are genito-urinary and are comparable to those following radical therapy, however at lower incidences. Does the SAG consider that Tookad VTP offers benefit to patients in terms of reduction in the severity and/ or duration of acute and chronic toxicity compared to: (1) active surveillance followed by radical therapy? (2) 'up-front' radical therapy?

Direct comparisons between active surveillance, radical therapy or Tookad VTP are not available and it is difficult to speculate on the merit of different strategies in terms of long terms outcomes. More generally, the usefulness of focal therapy compared to other options in terms of long-term outcomes is currently unknown.

Delaying radical therapy is considered of clinical importance for some patients as radical therapy is associated with a decrease in HRQoL for some patients, although the (short-lived) side-effects of focal therapy should be taken into account. However, even more clinically important would be avoiding radical therapy, an attractive potential of focal therapy. Currently, it is not possible to assess to what extent focal therapy is able to eradicate (long term, e.g., 10 years or longer) the disease, due to short follow-up and limited evaluation of the effect of therapy. Until such effect is demonstrated the uncertainty about potential detrimental effects in the long term plays a key role.

The SAG had divergent views about the overall benefits and risks of Tookad VTP. According to the prevalent view, Tookad VTP therapy was associated with short-term benefits some (deferring the need for radical therapy by median difference of about 14 months compared to active surveillance), short-term risks, and in the short term there seemed to be a positive benefit-risk balance. However, in the context of low-risk prostate cancer, with active surveillance being a valid management option and the existence of effective treatments in case of progression, it is the long-term benefits (and risks), which bear more weight in the overall benefit-risk assessment. Prostate cancer can be a multifocal disease but the study presented did not use current optimal imaging and biopsy strategies. Furthermore, the follow-up of available studies with Tookad VTP is of insufficient duration to understand the long-term effects given the complex and heterogeneous prostate cancer biology requiring 10 or more years of follow-up. Without this information, it is impossible to make informed treatment decisions. Based on the available data, it is not yet known, whether it is possible to avoid radical therapy for ever at least in a part of the patients. Possible risks identified with Tookad VTP include the risk of hampering the efficacy and safety subsequent radical treatments. Unfortunately, there was no complete collection of the safety data post salvage RT in the study, the safety data were reported using imputation from other studies. The data provided about prostatectomy were in a limited number of patients. Likewise, data on intention to treat that included the impact of radical treatment were not available. To address the potential long-term outcome risks, it is necessary to study long-term (e.g., 10-year or longer, since very few events are expected before that time) distant metastasis free survival or need for systemic therapy, in a study with adequate sample size to detect clinically relevant differences. This is in line with the requirement of EMA guidelines that in the case of intermediate endpoints (e.g., PFS), request some assurance that long-term outcomes are not jeopardised, as well as EMA scientific advice for Tookad VTP ("Continued follow-up of these patients to assess clinical outcome, in particular overall survival, should be implemented, even if such data are immature at the time of an initial submission"). Unfortunately, no data are currently available to assess the long-term outcomes in the two groups. For a majority of SAG members, this risk was considered unjustified, in the absence of efficacy data showing at least non-inferiority

of the approach in terms of long-term outcome. Given the existence of highly effective alternative therapy (radical therapy) and the fact that the disease is not rare, a risk of compromising long-term outcome was not considered justified. The existence of a small study assessing the feasibility of radical surgery following focal therapy was not sufficiently reassuring in this respect (Lebdai et al.).

However, according to some SAG members, like other focal therapies that are currently in use (e.g., cryotherapy), Tookad VTP could be a useful procedure for low risk patients wishing to defer radical therapy being fully informed about potential risks and uncertainties. Tookad VTP also avoids the need for short-term or rather early radical therapy in more than half of the patients at 2 years. There is also a potential that a still undefined number of patients will forever avoid radical therapy and its well documented early and late adverse effects. The long-term results are not yet available; however, there are enough long-term data of other focal therapies like cryotherapy and high-intensity focused ultrasound (HIFU), showing that a majority of patients can be cured if properly selected. When it comes to genito-urinary toxicity, the adverse effect of Tookad VTP occurred at a much lower incidence than after radical therapy and patients recovered rapidly once the treatment has been delivered. According to this view, long-term outcome studies are not considered feasible (and are not required for non-drug approaches that are currently in use) as they are not considered commercially attractive and the technology might become redundant due to evolving diagnostic standards. Although the uncertainty associated with lack of long-term outcome data is acknowledged, available surgical outcome data assessing the feasibility of radical therapy following Tookad VTB did not raise concerns (Lebdai et al.). Thus, the uncertainty could be acceptable as long as the data were collected post-marketing and clear communications of benefits and uncertainties to a selected population.

Patient management post Tookad VTP is not clear. Follow-up PSA measurements may be difficult to interpret due to the remaining prostate tissue. There is at least a theoretical risk that the sensitivity of follow-up prostate biopsies could be reduced and that residual tumour cells within the treated area could become more aggressive. Local fibrosis may impair the ability to later successfully undergo treatment with curative intent.

The SAG was asked to discuss these factors and whether they influence the population for which Tookad VTP could be indicated. How should these risks be monitored? Can the SAG propose an algorithm for patient follow-up in the months and years post Tookad VTP?

According to a majority of SAG members, in the absence of long-term data, it is not possible to exclude a risk of detriment in terms of long-term outcome associated with Tookad VTB. In the absence of such reassurance, given the availability of highly efficacious treatment (radical therapy) and valid management options such as active surveillance, it is difficult to accept the risk of a detriment in long-term outcomes or to minimise it through intense monitoring. Equally, it is not possible to propose an evidence-based algorithm for patient follow-up after Tookad VTP.

However, some SAG members disagreed (see answer to questions No. 1). Concerning detriment in terms of long-term outcome, the only relevant detriment that could be caused is a more tedious or difficult radical prostatectomy but as discussed above, this has not been objectivated or shown in the data available. According to this view, some uncertainties remain, but patients with low risk Gleason score 3+3 disease, excluding very low risk disease, could benefit from this focal therapy (low risk disease defined as stage T1c/T2a, prostate specific antigen 10 ng/ml or less, and Gleason score 6 or less; very low risk disease defined as stage T1c, prostate specific antigen density 0.15 or less, Gleason score 6 or less, 2 or fewer positive biopsy cores, 50% or less cancer involvement per core). Further analysis of the available data might guide the exploration of the population for which Tookad VTP could be indicated, fully acknowledging the methodological drawbacks of exploratory subgroup analysis. The trial only included unilateral ablation and this should likely be reflected in a potential indication. Diagnostic workup should be based on current standards such as modern multi-parametric MRI-based strategies and template based biopsy procedures. This treatment option might be preferred by low risk patients who prefer active treatment due to personal circumstances, e.g., direct personal experience of close relative (father, grandfather) dying at young age of metastatic prostate cancer.

Considering current treatment paradigms for localised low risk prostate cancer, can the SAG suggest a patient population in whom Tookad VTP would represent a suitable therapeutic option?

For a majority of SAG members, the risk of a detriment in long-term outcome was considered unknown in this low risk population, and this is a concern given the availability of alternative management options and treatments, despite the high rate of early and longstanding adverse effects associated with radical treatment.

However, some SAG members disagreed, and considered that Tookad VTP could be a useful procedure for higher risk patients (in this low risk group) who prefer deferring radical therapy and potentially avoiding it altogether (see answer to questions No. 1 and 2). According to this view, the risk of detriment long term was considered acceptable.

2.5.4. Conclusions on the clinical efficacy

The presented efficacy results showed a statistically significant improvement for Tookad VTP over active surveillance for both co-primary endpoints and the main secondary endpoints (initiation of radical therapy and tumour burden) in the ITT population. In the targeted population, the observed results were better for the key endpoints used for the comparison of Tookad vs. Active Surveillance. These results are considered clinically relevant for patients with low risk prostate cancer (excluding very low risk) wishing to defer radical therapy being fully informed about potential risks and uncertainties (see RMP).

The risk of/time to receiving radical therapy (RT), with its consequent ADRs, was also substantially delayed, although the reduction in risk of radical therapy and genitourinary toxicities has to be considered with caution in M24 to M48 due to a potential for under-detection of the need of radical therapy.

Considering the short duration of follow-up and the potential risk that Tookad VPT compromises the results of local treatment with curative intent, the CHMP considers the following measures necessary to address issues related to efficacy:

Post-authorisation efficacy study (PAES): In order to further investigate long-term efficacy of Tookad and its impact on disease progression including potential impact on the efficacy of subsequent radical therapy in patients with low risk prostate cancer as well as further characterise the long term safety of Tookad, the MAH should submit the results of a randomised phase 3 study in patients with localised prostate cancer compared to active surveillance (7-year follow-up study including in an depth biopsy study) (PCM301 FU5).

Submission of final study results: 31/12/2020.

Post-authorisation efficacy study (PAES): In order to further investigate long-term efficacy of Tookad and its impact on disease progression including potential impact on the efficacy of subsequent radical therapy in patients with low risk prostate cancer (excluding very low risk) as well as further characterise the long term safety of Tookad, the MAH should conduct and submit the results of a long-term observational cohort study of patients with unilateral low risk localised prostate cancer treated with Tookad VTP (CLIN1501 PCM401).

Submission of final study results: 31/12/2025.

2.6. Clinical safety

Patient exposure

Up to 1 October 2015, 517 subjects had received Tookad in 11 clinical trials.

- Phase 1: 42 healthy male volunteers - 1 study
- Phase 2: age related macular degeneration (AMD) - 2 studies (32 patients); inoperable cholangiocarcinoma -1 study (7 patients); obstructing endobronchial non-small cell lung cancer -1 study (3 patients) and renal carcinoma – 1 study (4 patients); localised prostate cancer - 3 studies:

  - PCM201: 40 patients, 4 retreated in same lobe, 1 in contralateral lobe

  - PCM202: 30 patients, 7 retreated in same lobe

  - PCM203: 85 patients, 6 retreated same lobe, 2 in contralateral lobe

- Phase 3 – localised prostate cancer - 2 studies

  - PCM301: 196 patients received Tookad, 62 treated in contralateral lobe, 11 retreated in same lobe and 2 later had bilateral treatment

  - PCM304: 78 patients received Tookad, 17 in contralateral lobe before Month 6, after Month 6 - 3 in previously treated lobe, 1 in contralateral lobe and 4 in both lobes.

One patient was granted access to Tookad D via a special permission programme in Panama, bringing the total to 518 subjects.

Table 58 Subject exposure across different dose ranges with Tookad

HUMAN EXPOSURE	1.25 mg/kg	2 mg/kg	2.5 mg/kg	4 mg/kg	5 mg/kg	6 mg/kg	7.5 mg/kg	10 mg/kg	15 mg/kg	Patients treated to date
HEALTHY SUBJECTS										
MLT101	6		6		12		6	6	6	42
PROSTATE CANCER										
PCM201		3		35		2				40
PCM202		9		21						30
PCM203				64*		21				85
PCM301				196						196
PCM304				78						78
Special permission: Panama				1						1
Total prostate cancer patients		12		395*		23				430
OTHER INDICATIONS										
MLT201	7		15							22
MLT202	0		10							10
CCM 201			3		4					7
LCM 201					3			0		3
KCM201		3		1						4
Total	**13**	**15**	**34**	**396**	**19**	**23**	**6**	**6**	**6**	**518**

* Three patients received 300 J/cm energy

WST 11 was given as a single 10 minute intravenous administration. Around 120 patients received a second Tookad infusion in the treatment of the same or the contralateral lobe.

The applicant presented a pooled analysis of the 398 patients in the ITT population who received the recommended dose of 4mg/kg Tookad and 200J/cm light. Of these 7 patients did not receive Tookad due to events occurring after the start of anaesthesia but before the administration of study drug. The mean amount of study medication per patient was 31.7mL (relative dose intensity 100%) with the first treatment, 31.6mL (relative dose intensity 100%) with a second VTP therapy and 32.1mL (relative dose intensity 100.1%) with retreatment.

Adverse events

Phase 1 Study

Single intravenous doses of WST11 were administered to 42 subjects. Eight subjects reported 9 treatment emergent adverse events during the study. Vasovagal syncope was the most frequently reported AE (3/9) experienced around 3 hours post injection; one subject in the 1.25mg/kg group experienced vasovagal syncope twice at a time interval of about 10 minutes; the other event was at the 5mg/kg dose. Other adverse events were linked to the intravenous administration and included hand paraesthesia (2.5mg/kg dose, 3 minutes post initiation of infusion) and injection site hypersensitivity (vein tingling with 15mg/kg dose 4 minutes post initiation of infusion) or were hypersensitivity type reactions, namely urticaria (5mg/kg dose 4 days post injection) and generalised pruritus (10mg/kg lasted for <4 days 1 week post injection).

One serious adverse event (photosensitisation-erythema) was reported for one subject in the 15 mg/kg dose group.

There was no relationship between the number of AEs and administered dose. There was no obvious trend with regards to mean systolic and diastolic blood pressure and the vasovagal events. Eleven subjects had ECG values out of normal range, judged not clinically significant. Measurement of QT interval and QTc (Bazett corrected) was automatically performed with manual over - reading of values over 440ms. Manual reading of QT was performed on 3 subjects pre-dose and 6 subjects post-dose. After manual reading only 1 QTc remained slightly long at 48 hours (431ms).

Pooled safety analysis of phase II and phase III patients treated with optimal drug and light doses

The optimal dose of drug and light in the treatment of localized prostate cancer has been determined as 4mg/kg of Tookad and a light intensity of 200 Joules per cm of fibre. Among the 429 patients treated during the five clinical studies in localized prostate cancer patients, the number of patients treated with doses and light intensities other than 4 mg/kg (i.e. 2 mg/kg or 6 mg/kg) and 200 J/cm (i.e. 300 J/cm) was very small with the exception of study PCM203 where 21 patients were treated with 6 mg/kg and 200 J/cm. However, there was no apparent relationship between higher dose and adverse events.

The use of Tookad is part of the VTP procedure that involves anaesthesia and the insertion of the light fibres as well as the activation of light; therefore, any patient who was in the clinical study who was expected to receive all of these components is included in the denominator for the safety overview. Of the 398 patients, only 391 received Tookad. The difference of 7 patients is due to events occurring after the start of anaesthesia but before the administration of the study drug.

In the pooled Phase 2/3 analysis, 1375 AEs were reported in 331 of 398 subjects (83.2%) of the safety population. Among them, 902 adverse events in 290 patients (72.9%) were considered as related to drug and/or device and/or VTP procedure. A total of 107 serious adverse events (SAE) in 79 patients (19.8%) were observed in this study, of which 51 in 41 patients (10.3%) were considered as related to drug and/or device and/or VTP procedure.

The most frequently reported adverse reactions in the Phase II and III clinical studies were urinary and reproductive system disorders: dysuria (25.1 %), erectile dysfunction (21.1 %), haematuria (19.6 %), perineal pain/haematoma (15.3 %), urinary retention (13.3 %), micturition urgency (9.0 %), pollakiuria (7.3 %), urinary tract infection (5.5 %), incontinence (5.3 %) and ejaculation failure (5.0 %).

In the table below an active surveillance group has been added as for Study PCM301 this was randomised between active intervention (VTP) and active surveillance.

Table 59 Summary Treatment Emergent Adverse Events in Phase II and Phase III Prostate Cancer Studies at the Recommended Dose

	PCM201	PCM202	PCM203	PCM301	PCM 304	All studies	Active Surveillance
Patients	N=37	N=21	N=62	N=197	N=81	N=398	N=207
Patients with at Least one TEAE	30(81.1%)	18(85.7%)	54(87.1%)	187(94.9%)	42(51.9%)	331(83.2%)	114(55.1)
Total number of TEAEs	113	140	154	854	114	1375	307
Patients with at Least one Serious TEAE	7(18.9%)	0	5 (8.1%)	59 (29.9%)	8 (9.9%)	79(19.8%)	21(10.1)
Total number of Serious TEAEs	7	0	8	84	8	107	25
Patients with at Least one AE Related to Study Drug, Device or procedure.	10(27.0%)	18(85.7%)	53(85.5%)	155(78.7%)	38(48.1%)	290(72.9%)	N/A
Total number of TEAEs Related to Study Drug, Device or procedure	25	97	114	518	105	902	N/A
Patients with at Least one TEAE Leading to Study Discontinuation/ Early Withdrawal	1 (2.7%)	0	1 (1.6%)	2 (1.0%)	3 (3.7%)	7 (1.8%)	1(0.5)
Patients with at Least one TEAE Leading to Death	0	0	0	1 (0.5%)	0	1 (0.3%)	0(0%)

N/A Not Applicable (The patients did not receive any active treatment and the study was open labelled)

The most common adverse events, regardless of causality, were seen in the SOC “Renal and Urinary Disorders” (58.5% of the patients) and in the SOC “Reproductive System and Breast Disorders” (46.2%). Those were mainly dysuria (28.4%), erectile dysfunction (25.6%), haematuria (20.6%), perineal pain (15.6%) and transient urinary retention (14.1%). These were most often considered related to the procedure and are a result of the need to put in the light fibres to the prostate (insertion of needles into the prostate, catheter etc.).

Table 60 Summary of Treatment Emergent Adverse Events (Number of patients) by System Organ Class and Preferred Term Occurring in > 2% of patients in Phase II and Phase III Prostate Cancer Studies at the Recommended Dose (independent of causality)

	PCM201	PCM202	PCM203	PCM301	PCM304	All studies
Patients	N=37	N=21	N=62	N=197	N=81	N=398
Renal And Urinary Disorders	13(35.1%)	17(81.0%)	40(64.5%)	133(67.5%)	30(37.0%)	233(58.5%)
Dysuria	8(21.6%)	9(42.9%)	24(38.7%)	54(27.4%)	18(22.2%)	113(28.4%)
Haematuria	5(13.5%)	7(33.3%)	7(11.3%)	56(28.4%)	7(8.6%)	82(20.6%)
Urinary Retention	2(5.4%)	6(28.6%)	5(8.1%)	32(16.2%)	11(13.6%)	56(14.1%)
Micturition Urgency	0	10(47.6%)	4(6.5%)	21(10.7%)	4(4.9%)	39(9.8%)
Pollakiuria	0	5(23.8%)	5(8.1%)	20(10.2%)	1(1.2%)	31(7.8%)
Urinary Incontinence	0	2(9.5%)	1 1.6%)	19(9.6%)	2(2.5%)	24(6.0%)
Urge Incontinence	0	0	1(1.6%)	8(4.1%)	1(1.2%)	10(2.5%)
Reproductive System And Breast Disorders	10(27.0%)	14(66.7%)	22(35.5%)	120(60.9%)	18(22.2%)	184(46.2%)
Erectile Dysfunction	4(10.8%)	6(28.6%)	11(17.7%)	74(37.6%)	7(8.6%)	102(25.6%)
Perineal Pain	4(10.8%)	9(42.9%)	7(11.3%)	30(15.2%)	12(14.8%)	62(15.6%)
Ejaculation Failure	0	0	2(3.2%)	16(8.1%)	2(2.5%)	20(5.0%)
Haematospermia	4(10.8%)	2(9.5%)	1(1.6%)	11(5.6%)	0	18(4.5%)
Prostatitis	1(2.7%)	1(4.8%)	3(4.8%)	10(5.1%)	2(2.5%)	17(4.3%)
Gastrointestinal Disorders	9(24.3%)	11(52.4%)	14(22.6%)	68(34.5%)	7(8.6%)	109(27.4%)
Constipation	1(2.7%)	2(9.5%)	7(11.3%)	9(4.6%)	3(3.7%)	22(5.5%)
Nausea	0	4(19.0%)	1(1.6%)	11(5.6%)	0	16(4.0%)
Haemorrhoids	4(10.8%)	0	2(3.2%)	6(3.0%)	0	12(3.0%)
Proctalgia	0	1(4.8%)	1(1.6%)	6(3.0%)	4(4.9%)	12(3.0%)
Infections And Infestations	6(16.2%)	2(9.5%)	11(17.7%)	58(29.4%)	7(8.6%)	84(21.1%)
Urinary Tract Infection	0	1(4.8%)	6(9.7%)	21(10.7%)	2(2.5%)	30(7.5%)
Orchitis	1(2.7%)	0	3(4.8%)	7(3.6%)	2(2.5%)	13(3.3%)
Bronchitis	2(5.4%)	0	1(1.6%)	6(3.0%)	0	9(2.3%)
Nasopharyngitis	0	1(4.8%)	0	8(4.1%)	0	9(2.3%)
Injury, Poisoning And Procedural Complications	6(16.2%)	2(9.5%)	1(1.6%)	36(18.3%)	3(3.7%)	48(12.1%)
Perineal Injury				15(7.6%)		15(3.8%)
Musculoskeletal And Connective Tissue Disorders	2(5.4%)	4(19.0%)	5(8.1%)	28(14.2%)	0	39(9.8%)
Back Pain	0	2(9.5%)	0	10(5.1%)	0	12(3.0%)
General Disorders And Administration Site Conditions	4(10.8%)	6(28.6%)	8(12.9%)	18(9.1%)	2(2.5%)	38(9.5%)
Pyrexia	0	2(9.5%)	1(1.6%)	4(2.0%)	2(2.5%)	9(2.3%)
Skin And Subcutaneous Tissue Disorders	2(5.4%)	5(23.8%)	9(14.5%)	13(6.6%)	9(11.1%)	38(9.5%)
Ecchymosis	0	4(19.0%)	0	1(0.5%)	9(11.1%)	14(3.5%)
Investigations	10(27.0%)	8(38.1%)	1(1.6%)	12(6.1%)	0	31(7.8%)
Fibrin D Dimer Increased	7(18.9%)	0	0	4(2.0%)	0	11(2.8%)
Vascular Disorders	1(2.7%)	2(9.5%)	2(3.2%)	20(10.2%)	0	25(6.3%)
Hypertension	0	1(4.8%)	0	9(4.6%)	0	10(2.5%)

The most frequent adverse events are presented below in descending order of frequency and the events that occurred in the active surveillance arm of study PCM301 are provided for reference. In the case of the active surveillance patients the adverse events were usually as a result of their prostate size or from biopsies that were not only part of the study but also part of routine active surveillance activities. Because of their nature and frequency and relatedness, certain adverse events have been identified as adverse events of special interest and marked with an (*) in the table below as these will be followed specifically for risk management purposes. In addition, AEs related to the VTP procedure are included.

Table 61 Summary of Frequency of Treatment Emergent Adverse Events by Preferred Term Occurring in ≥ 2% of Patients in Prostate Cancer Studies at the Recommended Dose

Preferred Term	Number of Patients with at least one Adverse Event		
	VTP (all cause) (N=398)	VTP (Related (N=398)	Active Surveillance (N=207)
Dysuria*	113(28.4%)	100(25.1%)	5 (2.4%)
Erectile dysfunction*	102(25.6%)	84(21.1%)	24 (11.6%)
Haematuria*	82(20.6%)	78(19.6%)	6 (2.9%)
Perineal pain*	62(15.6%)	61(15.3%)	1 (0.5%)
Urinary retention*	56(14.1%)	53(13.3%)	2 (1.0%)
Micturition urgency*	39(9.8%)	36(9.0%)	2 (1.0%)
Pollakiuria*	31(7.8%)	29(7.3%)	6 (2.9%)
Urinary tract infection*	30(7.5%)	22(5.5%)	9 (4.3%)
Urinary incontinence*	24(6.0%)	21(5.3%)	10 (4.8%)
Constipation	22(5.5%)		
Ejaculation failure*	20(5.0%)	20(5.0%)	1 (0.5%)
Haematospermia	18(4.5%)	15(3.8%)	
Prostatitis	17(4.3%)	13(3.3%)	
Nausea	16(4.0%)	9(2.3%)	
Perineal injury	15(3.8%)	15(3.8%)	
Ecchymosis	14(3.5%)	14(3.5%)	
Orchitis	13(3.3%)	8(2.0%)	
Haemorrhoids	12(3.0%)	11(2.8%)	
Proctalgia	12(3.0%)	10(2.5%)	
Back pain	12(3.0%)		
Fibrin D dimer increased	11(2.8%)	9(2.3%)	
Urge incontinence	10(2.5%)		
Hypertension	10(2.5%)		
Pyrexia	9(2.3%)		
Bronchitis	9(2.3%)		
Nasopharyngitis	9(2.3%)		
Abdominal pain	8(2.0%)		
Diarrhoea	8(2.0%)		
Inguinal hernia	8(2.0%)		
Vomiting	8(2.0%)		

* AESI

Erectile dysfunction

In the Phase III European study, 60 (30.5 %) of patients in the Tookad -VTP arm experienced erectile dysfunction and 16 (8.1 %) experienced ejaculation failure. 53 (26.9 %) patients experienced erectile dysfunction for more than 6 months, including 34 (17.3 %) patients in whom the erectile dysfunction had not resolved at the end of the study. When the analysis was restricted to patients that underwent unilateral VTP, 33 (16.8 %) patients experienced erectile dysfunction for more than 6 months, including 17 (8.6 %) patients in whom the erectile dysfunction had not resolved at the end of the study.

Urinary retention

In the Phase III European study, 30 (15.2 %) patients experienced urinary retention. The median time to onset of urinary retention was 3 days (1-417). The median duration was 10 days (1-344).

Genito-urinary infections

The most common infections are orchitis, epididymitis and urinary tract infections including cystitis. In the Phase III European study, 20 (10.2 %) patients in the Tookad -VTP arm experienced genito-urinary infection. In 5 (2.5 %) patients, the infection was considered serious. The median time to onset of genito-urinary infections was 22.5 days (4-360). The median duration was 21 days (4-197).

Urinary incontinence

In the Phase III European study, 25 (12.7 %) patients experienced urinary incontinence (including incontinence, stress urinary incontinence and urge incontinence). The median time to onset of urinary incontinence was 4 days (1-142). In 18 patients the adverse event resolved with a median duration of 63.5 days (1-360), and the adverse event was still ongoing at the end of the study for 7 patients. Only 1 (0.5 %) patient had a severe (Grade 3) urinary incontinence. None of these patients required an operation for incontinence.

Perineal injury, perineal pain and prostatitis

Perineal injury and perineal pain occurred in 46 (23.4 %) patients in the controlled Phase III European study. In some cases pain relief was required for perineal pain or anorectal discomfort. One patient had Grade 3 perineal pain that started 35 weeks after the VTP procedure, and lasted for about 35 weeks before resolving without sequelae.

Prostatitis occurred in 7 (3.6 %) patients in the controlled Phase III European study. One patient had Grade 3 prostatitis considered as serious that started 4 days after the VTP procedure, and lasted for 31 days before resolving without sequelae.

Urethral stenosis

In the pivotal Phase III European study, moderate or severe urethral stenosis developed in 2 (1.0 %) patients 5 to 6 months post-procedure. This required urethral dilatation (see section 4.4).

Extraprostatic necrosis

Two cases of excessive extraprostatic necrosis occurred due to incorrect laser calibration without clinical sequelae. One case of external urethral fistula occurred due to fibre misplacement (see section 4.4).

Phototoxicity

In a patient treated at 2 mg/kg of Tookad, one case of Grade 3 ischaemic optic neuropathy was reported 33 days after the VTP procedure. This resolved with a small defect in the visual field.

Prostatic abscess

One serious adverse event of prostatic abscess which was considered severe was reported in the study performed in Latin America in a patient who had a unilateral VTP procedure. The case resolved within three days.

Bilateral and unilateral treatment

Table 62 Summary of TEAEs Related to Study Drug, Study Device or VTP Procedure for Unilateral and Bilateral Treatment by System Organ Class and Preferred Term Occurring in ≥5% of patients in Either Group for All Studies (Pooled Phase II and III) in Prostate Cancer at the Recommended Dose

	Total number of patients with at least one adverse event	
	Unilateral N=274	**Bilateral N=117**
TEAE		
Total no. of patients with ≥1 AE	223 (81.4%)	104 (88.9%)
Total no. of AEs	927	444
Serious TEAE		
Total no. of patients with ≥1 AE	47(17.2%)	31(26.5%)
Total no. of AEs	66	40
All System Organ Classes	**196 (71.5%)**	**92 (78.6%)**
Gastrointestinal disorders	**42 (15.3%)**	**22 (18.8%)**
Haemorrhoids	5 (1.8%)	6 (5.1%)
Infections and infestations	**23 (8.4%)**	**9 (7.7%)**
Urinary tract infection	15 (5.5%)	7 (6.0%)
Injury, poisoning and procedural	**21 (7.7%)**	**14 (12.0%)**
Perineal injury	6 (2.2%)	9 (7.7%)
Renal and urinary disorders	**144 (52.6%)**	**74 (63.2%)**
Dysuria	70 (25.5%)	30 (25.6%)
Haematuria	51 (18.6%)	27 (23.1%)
Urinary retention	29 (10.6%)	24 (20.5%)
Micturition urgency	22 (8.0%)	14 (12.0%)
Pollakiuria	22 (8.0%)	7 (6.0%)
Urinary incontinence	13 (4.7%)	8 (6.8%)
Reproductive system and breast	**107 (39.1%)**	**57 (48.7%)**
Erectile dysfunction	49 (17.9%)	35 (29.9%)
Perineal pain	46 (16.8%)	15 (12.8%)
Ejaculation failure	11 (4.0%)	9 (7.7%)

Retreatment

Only 35 patients underwent retreatment in the same lobe that had originally been treated so single events had a more profound effect on the overall percentage. The retreatment procedures generally occurred after examination of the first on study biopsy (6 months for the Phase IIs and PCM304 and 12 months for PCM301). There was a slight increase in the proportion of TEAEs and serious TEAEs in patients retreated compared to those who were only treated once [TEAE: 33/35 (94.3%) vs. 294/356 (82.6%); serious TEAEs 9/35 (25.7%) vs. 69/356 (19.4%)]. The main increases were micturition urgency which increased from 1 (2.9%) to 6 (17.1%) events and proctalgia, post-procedure haematuria, asthenia and pain that increased from 0 to 2 events.

Non-study post-authorisation exposure and "special permission" cases

A single patient was granted "special permission" status to receive Tookad experienced severe extra-prostatic necrosis with urinary fistula following treatment resulting in hospitalisation. The event was considered to be probably related to the study medication, procedure and device as all three aspects of the procedure may be implicated in the extraprostatic necrosis; however, examination of the ultrasound scans taken at the time of the procedure suggested that the lengths of the fibres were significantly longer than the ones recommended by the treatment guidance performed at the beginning of the procedure, which would have been responsible for extra prostatic exposure and subsequent necrosis.

Adverse drug reactions

Table 63 Summary of adverse reactions considered related to Tookad and/or the study device and/or the study procedure in the pooled safety analysis (N=398)

System Organ Class	Frequency category	Frequency*	Adverse reaction
Infections and infestations	Common	32 patients (8.0 %)	Genito-urinary tract infection[1]
	Uncommon	1 patient (0.3%)	Prostatic abscess
Psychiatric disorders	Uncommon	3 patients (0.8 %)	Libido decreased
		1 patient (0.3%)	Affective disorder
		1 patient (0.3%)	Encopresis
Nervous system disorders	Uncommon	3 patients (0.8 %)	Headache
		2 patients (0.5%)	Dizziness
		2 patients (0.5%)	Sciatica
		1 patient (0.3%)	Sensory disturbance
		1 patient (0.3%)	Formication
Eye disorders	Uncommon	1 patient (0.3%)	Eye irritation
		1 patient (0.3%)	Photophobia
Vascular disorders	Common	4 patients (1.0 %)	Haematoma
		4 patients (1.0 %)	Hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	1 patient (0.3%)	Exertional dyspnoea
Gastrointestinal disorders	Common	11 patients (2.8 %)	Haemorrhoids
		20 patients (5.0 %)	Anorectal discomfort[2]
		7 patients (1.8 %)	Abdominal pain
		7 patients (1.8 %)	Rectal haemorrhage[3]
	Uncommon	1 patient (0.3%)	Abdominal discomfort
		1 patient (0.3%)	Abnormal faeces
		1 patient (0.3%)	Diarrhoea
Hepatobiliary disorders	Common	5 patients (1.3 %)	Hepatotoxicity[4]
Skin and subcutaneous tissue disorders	Common	14 patients (3.5 %)	Ecchymosis
	Uncommon	3 patients (0.8 %)	Rash
		2 patients (0.5%)	Erythema
		1 patient (0.3%)	Dry skin
		1 patient (0.3%)	Pruritus
		1 patient (0.3%)	Skin depigmentation
		1 patient (0.3%)	Skin reaction
Muscular and	Common	4 patients (1.0 %)	Back pain[5]

System Organ Class	Frequency category	Frequency*	Adverse reaction
connective tissue disorders	Uncommon	2 patients (0.5%)	Groin pain
		2 patients (0.5%)	Muscle haemorrhage
		1 patient (0.3%)	Haemarthrosis
		1 patient (0.3%)	Musculoskeletal pain
		1 patient (0.3%)	Pain in extremity
Renal and urinary disorders	Very common	54 patients (13.6 %)	Urinary retention
		81 patients (20.4 %)	Haematuria
		108 patients (27.1 %)	Dysuria[6]
		65 patients (16.3 %)	Micturition disorders[7]
	Common	4 patients (1.0 %)	Urethral stenosis
		35 patients (8.8 %)	Urinary incontinence[8]
	Uncommon	1 patient (0.3%)	Ureteric haemorrhage
		1 patient (0.3%)	Urethral haemorrhage
		2 patients (0.5%)	Urinary tract disorders
Reproductive system and breast disorders	Very common	65 patients (16.3 %)	Perineal pain[9]
		97 patients (24.4 %)	Male sexual dysfunction[10]
	Common	13 patients (3.3 %)	Prostatitis
		15 patients (3.8 %)	Genital pain[11]
		11 patients (2.8 %)	Prostatic pain[12]
		15 patients (3.8 %)	Haematospermia
	Uncommon	1 patient (0.3%)	Genital haemorrhage
		2 patients (0.5%)	Penile swelling[13]
		1 patient (0.3%)	Prostatic haemorrhage
		1 patient (0.3%)	Testicular swelling
General disorders and administration site conditions	Common	4 patients (1.0 %)	Fatigue
	Uncommon	2 patients (0.5%)	Asthenia
		2 patients (0.5%)	Catheter site pain
		2 patients (0.5%)	Laser device failure
		1 patient (0.3%)	Infusion site bruising
		1 patient (0.3%)	Nodule
		1 patient (0.3%)	Pain
		1 patient (0.3%)	Application site erythema
Investigations	Common	9 patients (2.3 %)	Abnormal clotting[14]
	Uncommon	2 patients (0.5%)	Blood lactate dehydrogenase increased
		2 patients (0.5%)	Blood triglyceride increased
		2 patients (0.5%)	Gamma-glutamyltransferase increased
		1 patient (0.3%)	Blood cholesterol increased

System Organ Class	Frequency category	Frequency*	Adverse reaction
		1 patient (0.3%)	Blood creatine phosphokinase increased
		1 patient (0.3%)	Blood potassium decreased
		1 patient (0.3%)	Low density lipoprotein increased
		1 patient (0.3%)	Neutrophil count increased
		1 patient (0.3%)	PSA increased
		1 patient (0.3%)	Weight decreased
		1 patient (0.3%)	White blood cell count increased
Injury, poisoning and procedural complications	Common	22 patients (5.5 %)	Perineal injury[15]
	Uncommon	1 patient (0.3%)	Surgical procedure repeated
		2 patients (0.5%)	Contusion
		2 patients (0.5%)	Post-procedural urine leak
		2 patients (0.5%)	Procedural pain
		1 patient (0.3%)	Post-procedural discharge
		1 patient (0.3%)	Fall

Serious adverse event/deaths/other significant events

Serious adverse events

A total of 107 serious adverse events (SAE) in 79 patients (19.8%) were observed in the five prostate cancer studies. Of these, 51 Serious Adverse Event (SAE) in 41 patients were considered to be related to the study drug and/or study device or the procedure and 58 were not related. In addition, 25 unrelated SAE were observed out of 207 patients in the Active Surveillance arm of study PCM301. Two SAEs in the active surveillance group followed radical prostatectomy (urinary tract infection and deep vein thrombosis) and there were two cases of pyrexia following biopsies. The other SAE that occurred more than once was myocardial infarction (3 patients). Those events considered related to study drug, study device or VTP procedure are summarized in the below table.

Table 64 Summary of Serious Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in Phase II and Phase III Prostate Cancer Studies at the Recommended Dose

	PCM201	PCM202	PCM203	PCM301	PCM304	All studies
Patients	**N=37**	**N=21**	**N=62**	**N=197**	**N=81**	**N=398**
Total number of patients with at least one related SAE	3 (8.1%)	0 (0.0%)	4 (6.5%)	30 (15.2%)	4 (4.9%)	41 (10.3%)
All related SAEs	3	0	5	39	4	51
Renal and Urinary Disorders	**0 (0.0%)**	**0 (0.0%)**	**2 (3.2%)**	**22 (11.2%)**	**2 (2.5%)**	**26 (6.5%)**
Dysuria				2		2 (0.5%)
Haematuria			1	3		4 (1.0%)
Urinary Retention				15	1	16 (4.0%)
Urethral stenosis			1	2	1	4 (1.0%)
Urinary Incontinence				1		1 (0.3%)
Reproductive System and Breast Disorders	**1 (2.7%)**	**0 (0.0%)**	**2 (3.2%)**	**3 (1.5%)**	**1 (1.2%)**	**7 (1.8%)**
Penile Pain				1		1 (0.3%)
Perineal Pain					1	1 (0.3%)
Pelvic Pain	1					1 (0.3%)
Prostatitis			2	2		4 (1.0%)
Gastrointestinal Disorders	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.5%)**	**0 (0.0%)**	**1 (0.3%)**
Vomiting				1		1 (0.3%)
Nausea				1		1 (0.3%)
Infections and Infestations	**0 (0.0%)**	**0 (0.0%)**	**1 (1.6%)**	**5 (2.5%)**	**1 (1.2%)**	**7 (1.8%)**
Urinary Tract Infection				3		3 (0.8%)
Orchitis			1	2		3 (0.8%)
Prostatic abscess					1	1 (0.3%)
Injury, Poisoning and Procedural Complications	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.5%)**	**0 (0.0%)**	**1 (0.3%)**
Surgical procedure repeated				1		1 (0.3%)
General Disorders and Administration Site Conditions	**2 (5.4%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (0.5%)**
Large extraprostatic necrosis	2					2 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.5%)**	**0 (0.0%)**	**1 (0.3%)**
Bronchospasm				1		1 (0.3%)
Investigations	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.0%)**	**0 (0.0%)**	**2 (0.5%)**
Body temperature increased				1		1 (0.3%)
Residual urine volume increased				1		1 (0.3%)
Vascular Disorders	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.5%)**	**0 (0.0%)**	**1 (0.3%)**
Perineal hematoma				1		1 (0.3%)
Nervous system disorders	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.5%)**	**0 (0.0%)**	**1 (0.3%)**
Transient global amnesia				1		1 (0.3%)

Table 65 Adverse Events by Severity – Safety Population – Study PCM301

Number of Subjects with AE in Category	VTP N = 197 n (%)	Active Surveillance N = 207 n (%)
Subjects with only Grade 1 (mild) AEs	49 (24.9)	42 (20.3)
Subjects with Grade 2 (moderate) AEs *as a maximum*	94 (47.7)	52 (25.1)
Subjects with Grade 3 (severe) AEs *as a maximum*	40 (20.3)	19 (9.2)
Subjects with Grade 4 (life-threatening) AEs *as a maximum*	3 (1.5)	1 (0.5)
Subjects with Grade 5 (death) AEs	1 (0.5)	0
Abbreviations: VTP = vascular-targeted photodynamic therapy.		

Table 66 Adverse Events Related to Drug, Device, or Procedure by Severity – Safety Population – Study PCM301

Number of Subjects with Related AE in Category	VTP N = 197 n (%)
Subjects with only Grade 1 (mild) AEs	54 (27.4)
Subjects with Grade 2 (moderate) AEs *as a maximum*	81 (41.1)
Subjects with Grade 3 (severe) AEs *as a maximum*	19 (9.6)
Subjects with Grade 4 (life-threatening) AEs as a maximum	1 (0.5)
Subjects with Grade 5 (death) AEs	0
AEs with assessments of very likely, probable or possible or with missing relationship are considered related.	

In the combined studies only 7% of adverse events were considered Grade 3, predominantly in the renal and reproductive SOC. At the recommended dose and light intensity in 398 patients there were five cases of Grade 3 dysuria (1.3%), two cases of haematuria (0.5%), four cases of urinary retention (1.0%), 3 cases of prostatitis, a Grade 3 prostatic abscess and 3 cases of Grade 3 erectile dysfunction (0.8%). Additionally there was one life-threatening (Grade 4) event (bronchospasm) related to an anaesthetic drug. One Grade 5 (myocardial infarct leading to death) was observed in the safety population at the recommended dose level.

In general, the pattern of SAEs followed that of non-serious AEs. In particular, 33 (66%) out of the 51 SAEs considered as related to study drug and/or device and/or procedure were genitourinary tract disorders in the Phase 2 and Phase 3 studies.

The most commonly observed related SAEs were urinary retentions (16 cases). Apart from two cases described below, all the cases of urinary retention started within the first 9 days following the surgical procedure and are probably secondary to the swelling of the prostate due to the insertion of the catheters needed to place the fibres in the prostate. They resolved in less than 7 days for eight of them, in 12, 15, 18, 25, 32 and 33 days for six others and in 43 days for a patient who had a medical history of benign prostatic hypertrophy. The two exceptions to the urinary retention being associated to the VTP procedure date were of a Mexican patient in whom the retention occurred 8 months after the VTP and had to be treated with a TURP and one other case in study PCM301 that started 13 months after the VTP procedure (and is classed as possibly related to the VTP procedure on the clinical database but unrelated in the SAE narrative).

Haematuria and dysuria are also a direct consequence of the procedure (traumatic catheterization, needles insertion, with a possible accidental puncture of the bladder or of the urethra), all of them resolved in within 3 days after the procedure.

There was one case of serious long-term urinary incontinence which occurred in a patient who previously had a TURP.

The four cases of urethral stenosis started within 2 to 6 months after the procedure. In some cases, it may be a late consequence of the necrosis, however, on some other cases, the bulbar location of the stenosis was more in favour of a urethral traumatism (e.g. catheterization). All of them resolved with a TURP. Prostatitis, urinary tract infections and orchitis were also seen in some patients.

Deaths

No deaths related to the study drug, the study device or the study procedure was reported in the five localized prostate cancer studies. A patient died of a myocardial infarction 34 weeks after receiving a single dose of Tookad in study PCM301. The event was deemed unrelated to drug, device or protocol procedure.

Laboratory findings

Haematology/ biochemistry

PCM201: D-dimer levels were increased from baseline at 4 hours post procedure and remained elevated at Day 4. This was considered to be related to the anaesthetic and the procedure (insertion of needles in the perineum). A decrease in fibrinogen was observed post procedure. Mean baseline value was 3.3g/L; it decreased to 2.4g/L (-0.9 mean change) 4 hours post procedure; returned to normal Day 2 and increased at 1 week to 5.3g/l (+2.0 mean change). The neutrophils showed the same pattern of increase as the D-dimers.

PCM301: No consistent difference between 2 groups except all subjects in the VTP arm had an elevated D-dimer (up to 20 x ULN) on the day after the VTP procedure. The DSMB reviewed the D-dimer results and did not consider them of clinical significance.

ECG Safety Report

An exploratory ECG safety study ECG (not specified in the SAP) was conducted in Study PCM 201. The appraisal was based on a qualitative analysis of the main ECG variables derived from manual reading of paper ECG recordings, namely changes to morphology, central tendency and outlier effects for heart rate, QT and QTc intervals. The results indicated a marked effect of anaesthesia on QTcF but within the limitations of the study, i.e., small patient numbers and no control group, no clinically relevant changes in QTcF were observed following treatment with WST11.

Time with toxicities

The Applicant has made an analysis of time with toxicity up to 48 months, using data available to date from the 5-year follow-up study. This analysis was extended to 48 months by restricting it only to patients who have completed the follow up study (i.e. those with visits at 36 and 48 months completed). This approach was preferred to avoid further extrapolations on patients with no or partial follow-up. Confidence intervals at M24 and M48 have been estimated using bootstrap with 1000 simulations.

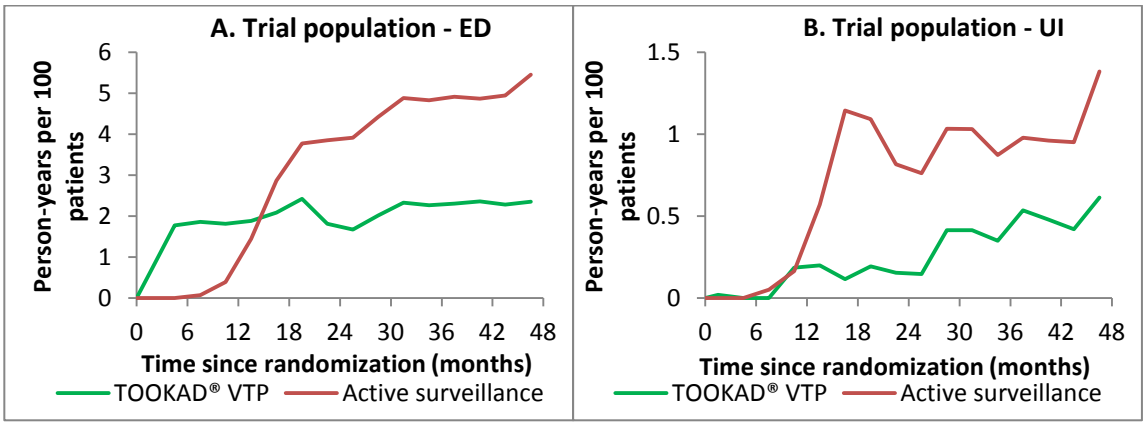


Figure 12 Time with genitourinary toxicities – Overall trial population. A. Erectile dysfunction; B. Urinary incontinence

The table below summarizes the ratios of areas under the curve between Tookad and Active Surveillance for each type of toxicity and their total, calculated over 24 and 48 months. Of note, the analysis over 48 months is restricted to those patients who have completed the 48 months follow-up.

Table 67 Time with genitourinary toxicity ratios – Overall trial population

	Ratio over 24 months (95% CI)	**Ratio over 48 months (95% CI)**
Total (ED+UI)	0.93 (0.47-1.03)	0.58 (0.27-0.64)
Erectile dysfunction (ED)	1.15 (0.57-1.29)	0.63 (0.28-0.69)
Urinary incontinence (UI)	0.23 (0.13-0.45)	0.36 (0.16-0.47)

The overall ratio is 0.93 (95% CI= 0.47-1.03) vs. 1.16 previously estimated. For ED: 1.15 (95% CI= 0.47-1.03) vs. 1.41 previously, and for UI: 0.23 (95% CI= 0.13-0.45) vs. 0.46 previously.

Due to the stable reduction in risk of RT between M24 and M48, the ratio of relative time with toxicity in the overall trial population is greater at M48 compared to M24: 0.58 overall (95% CI: 0.27-0.64), with 0.63 for ED (95% CI: 0.28-0.69) and 0.36 for UI (95% CI: 0.16-0.47).

Time with toxicities - Analysis in target population

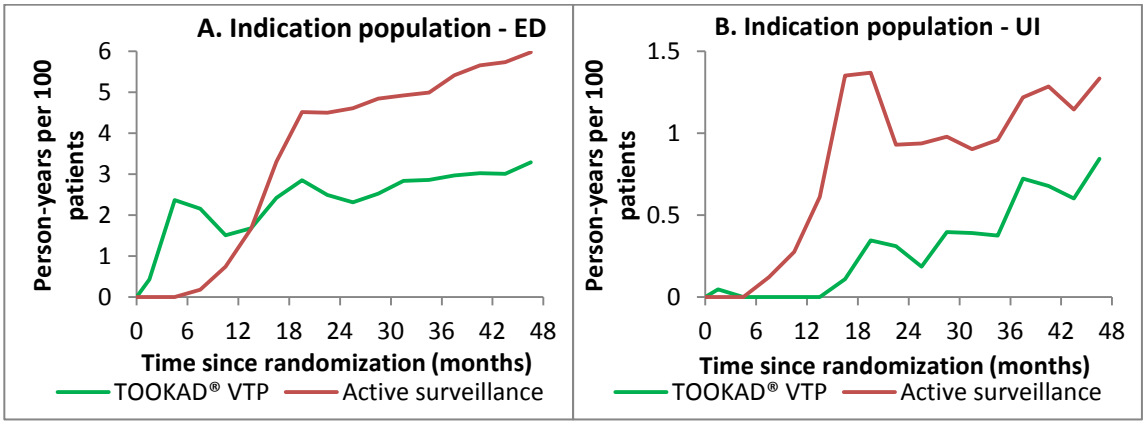


Figure 13 Time with genitourinary toxicities – indication population. A. Erectile dysfunction; B. Urinary incontinence

Table 68 Time with genitourinary toxicity ratios – indication population without censoring of patients with 2nd VTP

	Ratio over 24 months (95% CI)	Ratio over 48 months (95% CI)
Total (ED+UI)	0.85 (0.37-1.18)	0.62 (0.23-0.83)
Erectile dysfunction (ED)	1.07 (0.49-1.60)	0.68 (0.23-0.91)
Urinary incontinence (UI)	0.17 (0.05-0.44)	0.37 (0.14-0.58)

Sensitivity analysis: impact of 2nd VTP in target population

Subjects who received a 2nd VTP were censored at time of 2nd VTP.

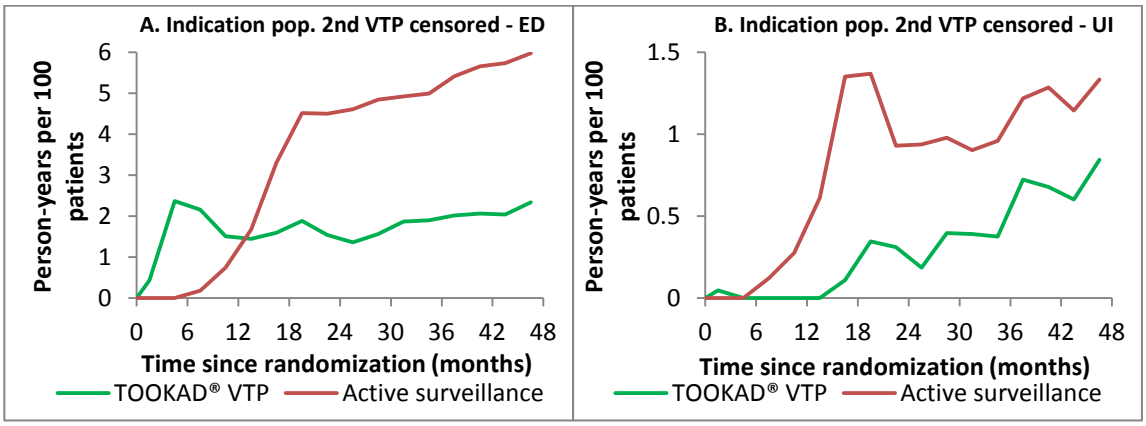


Figure 14 Time with genitourinary toxicities – indication population with censoring of patients with 2nd VTP. A. Erectile dysfunction; B. Urinary incontinence

Table 69: Time with genitourinary toxicity ratios – indication population with censoring of patients with 2nd VTP

	Ratio over 24 months (95% CI)	Ratio over 48 months (95% CI)
Total (ED+UI)	0.70 (0.34-1.22)	0.47 (0.16-0.66)
Erectile dysfunction (ED)	0.87 (0.43-1.59)	0.49 (0.15-0.70)
Urinary incontinence (UI)	0.17 (0.04-0.47)	0.37 (0.14-0.63)

The Applicant also conducted a further analysis of time with toxicity in the indication sub-population without imputation of toxicities from ProtecT after radical therapy events.

- 80 and 78 patients were included in the analysis between M0 and M24 respectively in the Tookad and the Active Surveillance arms, and 52 and 44 patients respectively in the period M24-M48
- In the Tookad arm, a total of 18 AEs were available in the M0-M24 period, with 15 pre-radical therapy and 3 post, and 15 EDs and 3 UIs. A total of 9 AEs were available in the M24-M48 period, with 5 pre-radical therapy and 4 post, and 6 EDs and 3 UIs
- In the Active Surveillance arm, a total of 12 AEs were available in the M0-M24 period, with 10 pre-radical therapy and 2 post, and 10 EDs and 2 UIs. A total of 6 AEs were available in the M24-M48 period, with 3 pre-radical therapy and 3 post, and 4 EDs and 2 UIs

Table 70 Genitourinary AEs of Grade ≥2 reported pre- and post-RT in PCM301 study – indication sub-population

	TOOKAD® VTP		Active Surveillance	
	M0-M24 N=80	M24-M48 N=52	M0-M24 N=78	M24-M48 N=44
Pre-radical therapy AEs				
• Erectile dysfunction (ED)	14	9	4	2
• Urinary incontinence (UI)	1	1	1	1
Post-radical therapy AEs				
• Erectile dysfunction (ED)	1	1	2	2
• Urinary incontinence (UI)	2	1	2	1
TOTAL	18	12	9	6

Safety profile in target population vs overall population

In the target population, for the Tookad VTP group, there was a 6.4% reduction in the frequency of Grade 3 events and an 8.0% increase in the frequency of Grade 2 events. When focusing only on the drug, device of procedure related events, the frequencies of the different severity grades are fairly consistent with a limited increase in Grade 2 events (4.7%) and limited decrease of Grade 3 events (3.3%).

The review of safety data in the overall population and target population showed similar profiles. The most noticeable differences were:

- A decrease of the overall incidence of SAEs in the Tookad arm for the indication sub-population compared to the overall population (26.6% vs. 30.5%)
- A decrease in the proportion of subjects with Grade 3-5 AEs (15.2% vs. 22.3%) and consequently an increase in the proportion of subjects with Grade 2 AEs (55.7% vs. 47.7%)
- The differences were smaller when considering only drug, device or VTP procedure-related SAEs or AEs
- Among the most frequent AEs (incidence ≥5% of subjects), the difference vs. the AS group became not statistically significant for micturition urgency, pollakiuria, and ejaculation failure and remained statistically significant for dysuria, haematuria, urinary retention, erectile dysfunction, and perineal pain.

Safety in special populations

Data were reviewed according to age (≤65 versus > 65 years of age) as well as for patients with co-existing hypertension or diabetes.

Elderly: Mean age was 64 years and in total 160 patients were > 65 years of age and 237 patients were ≤ 65 years of age. The oldest patient was 85 years old so the applicant has set no upper age limit provided that the patient is fit for general anaesthetic. Overall there was no difference in the occurrence of adverse events (all cause or related) between the 2 categories [subjects with at least 1 related AE 174/237 (73.4%) vs. 116/160 (72.5%)]. However, more patients were hospitalised for AEs in the older age group [SAEs 37/237 (15.6%) vs. 41/160 (25.6%)]. Certain events occurred more frequently in the different age categories – bradycardia, diarrhoea, inguinal hernia, epididymitis, scrotal injury, dizziness and depression in the elderly; perineal pain, ejaculation failure and increased d-dimer in younger patients.

Table 71 Pooled analysis - Summary of Treatment Emergent Adverse Events (TEAE) by age categories

Age category (year) **Number of patients (%)** **Number of events**	**< 65** **n=212**	**65-74** **n=166**	**75-84** **n=18**	**> 85** **n=1**	**Missing** **n=1**	**Overall** **n=398**
TEAE	175 (82.5%) 695	141 (84.9%) 612	13 (72.2%) 63	1 (100%) 4	1 (100%) 1	331 (83.2%) 1375
Serious TEAE	32 (15.1%) 38	39 (23.5%) 54	6 (33.3%) 12	1 (100%) 2	1 (100%) 1	79 (19.8%) 107
TEAE leading to discontinuation	2 (0.9%) 2	4 (2.4%) 4	0 0	0 0	1 (100%) 1	7 (1.8%) 7
TEAE related to drug, device or procedure	155 (73.1%) 480	122 (73.5%) 382	13 (72.2%) 40	0 0	0 0	290 (72.9%) 902
TEAE leading to death	1(0.5%) 1	0 0	0 0	0 0	0 0	1 (0.3%) 1

Table72 Pooled analysis – Number of TEAE by SOC and by age category (SOC with AEs in > 1% of patients)

Age category (year) Number of patients (%)	< 65 n=212	65-74 n=166	75-84 n=18	> 85 n=1	Missing n=1	Overall n=398
Renal and urinary disorders	127 (59.9%)	98 (59.0%)	8 (44.4%)	0	0	233 (58.5%)
Reproductive system and breast disorders	102 (48.1%)	74 (44.6%)	7 (38.9%)	(100%)	0	184 (46.2%)
Gastrointestinal disorders	51 (24.1%)	51 (30.7%)	6 (33.3%)	1 (100%)	0	109 (27.4%)
Infections and infestations	42 (20.3%)	33 (19.9%)	7 (38.9%)	1 (100%)	0	84 (21.1%)
Injury, poisoning and procedural complications	21 (9.9%)	21 (12.7%)	6 (33.3%)	0	0	48 (12.1%)
Musculoskeletal and connective tissue disorders	20 (9.4%)	18 (10.8%)	0	1 (100%)	0	39 (9.8%)
General disorders and administration site conditions	18 (8.5%)	19 (11.4%)	1 (5.6%)	0	0	38 (9.5%)
Skin and subcutaneous tissue disorders	21 (9.9%)	16 (9.6%)	1 (5.6%)	0	0	38 (9.5%)
Nervous system disorders	11 (5.2%)	21 (12.7%)	2 (11.1%)	0	0	34 (8.5%)
Investigations	20 (9.4%)	10 (6.0%)	1 (5.6%)	0	0	31 (7.8%)
Vascular disorders	13 (6.1%)	12 (7.2%)	0	0	0	25 (6.3%)
Psychiatric disorders	10 (4.7%)	8 (4.8%)	2 (11.1%)	0	0	20 (5.0%)
Respiratory, thoracic and mediastinal disorders	8 (3.8%)	9 (5.4%)	2 (11.1%)	0	0	19 (4.8%)
Surgical and medical procedures	12 (5.7%)	5 (3.0%)	2 (11.1%)	0	0	19 (4.8%)
Cardiac disorders	6 (2.8%)	4 (2.4%)	1 (5.6%)	0	0	11 (2.8%)

Age category (year) Number of patients (%)	< 65 n=212	65-74 n=166	75-84 n=18	> 85 n=1	Missing n=1	Overall n=398
Eye disorders	3 (1.4%)	7 (4.2%)	1 (5.6%)	0	0	11 (2.8%)
Metabolism and nutrition disorders	3 (1.4%)	6 (3.6%)	1 (5.6%)	0	0	10 (2.5%)
Neoplasm benign, malignant and unspecified	5 (2.4%)	4 (2.4%	1 (5.6%)	0	0	10 (2.5%)
Immune system disorders	1 (0.5%)	5 (3.0%)	0	0	1 (100%)	7 (1.8%)

Patients with co-morbidities

Hypertension: Around 40% of patients from the pooled analysis had co-existing hypertension (n=158). Overall the proportion of patients with at least 1 TEAE or related TEAE was similar in the 2 groups [≥1 TEAE 135/158 (85.4%) vs. 196/240 (81.7%); related TEAE 118/ 158 (74.7%) vs. 172/240 (71.7%)]. Serious TEAEs were more frequent in those with hypertension [42/158 (26.6%) vs. 37/240 (15.4%)]. In terms of all cause adverse events between the 2 groups there were no consistent differences but infections and infestations appeared higher in those with hypertension.

Diabetes: Only a few patients had diabetes (n=45) so it is difficult to compare individual AEs for incidence. The incidence of TEAEs and serious TEAEs were similar between those with and without diabetes.

Patients with hepatic/renal impairment

No safety data in hepatic/ renal impairment has been submitted.

Safety related to drug-drug interactions and other interactions

No safety data were submitted.

Discontinuation due to adverse events

Overall 7 patients were withdrawn from the studies due to AEs. In the Phase II prostate cancer studies and in study PCM 301 the withdrawals were due to AEs deemed unrelated to the study drug. The patient in PCM201 was withdrawn due to an ECG change, in PCM203 due to hypotension and the 2 patients in PCM 301 due to myocardial infarction 9.5 months post Tookad and anaphylactic reaction to anaesthesia.

Three patients were withdrawn because of an AE in study PCM304. One patient had a stroke (unrelated); one withdrew consent after experiencing decreased erectile function and one was withdrawn to undergo a TURP for urethral stenosis.

Post marketing experience

As of 29 September 2016, 38 patients have been treated as part of a special authorisation programme or post-marketing (Mexico). Of these 38 patients, 6 patients experienced a total of 7 AEs, 4 considered serious. No AEs have been reported from the patients treated in Mexico. There were 3 events of orchitis, 3 of urinary retention and 1 extraprostatic necrosis. All of the events were considered to be related to the VTP procedure and were Grade 2 or 3 in severity. These AEs are already covered in the product information.

2.6.1. Discussion on clinical safety

The pooled analysis was adequately performed in the 398 ITT population receiving the recommended dose of 4 mg/kg Tookad and 200 J/cm light. The small number of subjects that did not receive the study drug is not expected to influence the results. Considering the number of subjects exposed to Tookad in the reported trials and the proportion of those patients that were treated with the proposed dose and light energy, there is sufficient patient exposure and data for an adequate safety evaluation.

The overall number of patients with adverse events was similar across all of the studies where patients received VTP except for the Latin American study (PCM304) where reporting of events appeared to be lower for both all cause and related events, however the pattern of adverse events was similar to the other studies. PCM 201 also reported lower events related to any part of the procedure than the other studies. Excluding PCM304 did not alter the frequency category in the SmPC or result in inclusion of additional ADRs (data not shown).

Given the nature of the treatment, it is not possible to single out the relation of the drug to the AE, as device and VTP procedure also have to be considered. The most common AEs were usually considered to be related to the procedure as a consequence of inserting optical fibres into the prostate and the consequent prostate inflammation and swelling e.g. dysuria, erectile dysfunction, haematuria, perineal pain and urinary retention all occurred in over 10% of patients. These mainly recovered within a few days without sequelae. Erectile function declined to Month 3 followed by stabilisation. These events are reflected in section 4.8 of the SmPC.

When given alone, as in the healthy volunteer study, Tookad is very well tolerated. Events reported in the 42 healthy volunteers were mainly vasovagal (3 events), tingling at the injection site within minutes of injection and urticaria/ pruritus that occurred about 4 days post injection. Discomfort on injection would not be captured in patients under general anaesthetic. Tookad can have a pH up to 9 which is at the limit of what can be infused through a peripheral line without causing vascular complications. In study PCM201, WST11 was infused through a fast-flowing peripheral line (antecubital catheter) or a central line. Good venous access will be required. Phlebitis does not appear to have been identified as a safety concern preclinically or clinically.

Considering the risk of phototoxicity with Tookad, precautions such as preventing exposure to bright light during the procedure and the need to wear clothes covering the skin and dark glasses for a day following injection are reflected in the SmPC to reduce the risk of any phototoxic reaction. Tookad's maximum absorption is in the near infrared domain (NIR) at 753 nm. Artificial light sources other than television are considered in the warnings (see SmPC section 4.4) but the risk is very low, if any, considering the light emitted spectrum for such devices. The half-life of Tookad D ranges from 1.14-1.70 hours in prostate cancer patients and so, unlike other photosensitising agents, these precautions do not have to be in place for more than 48 hours. As no true phototoxic events have been reported this suggests that the precautions recommended shielding the patients from light except for the target tissue have been successful. Photosensitivity is an important identified risk in the RMP. The Guideline for Physician that will be put in place includes guidance for light protection.

A case of visual impairment (PCM201) and a case of photophobia/ eye irritation (PCM301) were reported. Although this followed bilateral therapy with 1 lobe treated with a single fibre delivering 300J/cm it is not clear how increased local light delivery would alter the likelihood of a systemic event. Eye irritation and photophobia are listed in the SmPC (see SmPC section 4.8).

Anal and rectal haemorrhages have also been reported and are included in the SmPC (see SmPC section 4.8). After a review of these cases as well as those of haemorrhoids it was considered that the most likely explanation, for those that occurred soon after VTP, was that manipulation of the rectal probe exacerbated pre-existing haemorrhoids which resulted in them being obvious to the patient or causing bleeding.

Unspecific adverse events probably linked to the general anaesthesia were also observed: transient global amnesia, bradycardia, sinus arrhythmia, atrial fibrillation, hypotension, bronchospasm, pharyngeal inflammation, respiratory tract congestion, nausea, vomiting, constipation, pyrexia, procedural hypotension. Some cases of hepatotoxicity (1.5 %), such as elevation of transaminases, were also reported. All of them were mild in intensity (see SmPC section 4.8).

Tookad is contraindicated in patients with any medical condition that precludes the administration of a general anaesthetic or invasive procedures (see SmPC section 4.3).

In the combined studies, only 7% of adverse events were considered Grade 3 predominantly in the renal and reproductive SOC. Additionally there was one life-threatening (Grade 4) event (bronchospasm) related to an anaesthetic drug used at the procedure. The risk of serious adverse events is not only related to the drug but also to device and procedure, which is performed under anaesthesia. There were also study associated SAE which are not related to treatment but to other study procedures, namely prostate biopsy.

The most common SAE was urinary retention and the risk was related to prostate volume. It was higher for volumes above 50 mL (data not shown) but no threshold could be identified. Patients with a history of urethral stricture or with urinary flow problems may be at increased risk of poor flow and urinary retention post the Tookad VTP procedure. Urinary retention immediately post procedure has been attributed to transient prostatic oedema and generally only short term recatheterisation was required. Poor urinary flow due to urethral stricture developed some months post procedure. In certain cases, the bulbar location suggested that the stenosis was caused by urinary catheterisation. In other cases, urethral stenosis may have been a late consequence of Tookad VTP induced necrosis. Although they were excluded from the clinical trials, there is a potential risk of increased stenosis post the Tookad VTP procedure for patients with pre-existing stenosis (see SmPC sections 4.4 and 4.8).

TEAEs and SAEs increased with bilateral and re-treatment, particularly micturition urgency and proctalgia, post-procedure haematuria, asthenia and pain. Bilateral and re-treatment are not recommended (see SmPC section 4.2).

Three cases of myocardial infarction were reported, one of them fatal. The time delay to VTP and the description of the cases support the conclusion as not related to the study drug, study device or procedure.

With careful treatment planning, the extent of necrosis should be confined to the prostate although some extra-prostatic necrosis is not unusual. There may be extra-prostatic necrosis in the peri-prostatic fat not associated with clinical symptoms. Excessive extraprostatic necrosis occurred as a result of incorrect calibration of the laser or placement of the light fibres (see SmPC section 4.8). In consequence there is a potential risk of damage to adjacent structures, such as the bladder and/or rectum, and development of a recto urethral or external fistula. A urinary fistula has occurred in one case due to incorrect fibre placement.

To date, although there has been evidence of some necrosis into muscles of the rectal wall in isolated cases, no recto-urethral fistula has been reported.

Urethral stenosis onset was within 2 to 6 months of VTP, possibly as a late consequence of necrosis or urethral trauma post catheterisation. All resolved with a TURP and it remains to be seen if more cases emerge with prolonged follow-up. Urethral stenosis is included as an important identified risk in the RMP.

Severe long-term urinary incontinence was observed in a patient who underwent a previous transurethral prostatectomy (TURP). This event was not considered to be related to a faulty procedure but rather the pre-existing damage to the internal urethral sphincter from the TURP. The Tookad -VTP procedure is contraindicated in patients with any previous prostatic interventions where the internal urinary sphincter may have been damaged, including trans-urethral resection of the prostate (TURP) for benign prostatic hypertrophy (see section 4.3). Long-term urinary incontinence is also included as an important potential risk in the RMP. The risk of sphincter damage can be minimised by careful planning of the fibre placement using the treatment guidance software.

The equipment should be carefully calibrated and the treatment guidance software should be used to reduce the risk of clinically significant extraprostatic necrosis (see SmPC section 4.4). Complications of extra-prostatic necrosis are included as important potential risk in the RMP. Long-term safety (including consequences of tissue necrosis) will be evaluated as part of the post authorisation efficacy studies (PAES) (see RMP).

Being an operator dependent treatment namely in the accuracy of light probe placing, with safety implications (extra-prostatic necrosis), the mention that Tookad should only be used by personnel trained in the Vascular-Targeted Photodynamic therapy (VTP) procedure in SmPC section 4.2 is adequate. Procedural related injuries and complications due to non-compliance with the device manufacturers' instructions and recommended guidance for the VTP procedure are included as important potential risk in the RMP. Both human error and device failure and are covered by this safety concern.

Patients with very low-risk prostate cancer have disease detected by prostate biopsy based upon serum PSA only, without detectable abnormality on digital rectal examination or imaging. To be classified as very low risk, such patients must have a tumour that is in histologic grade group 1 (Gleason score ≤6) on biopsy and a serum PSA <10 ng/mL. Furthermore, the extent of disease within the prostate must be limited (i.e., fewer than three positive biopsy cores with less than 50 percent involvement in any one core and a PSA density less than 0.15 ng/mL/gram). In this indolent disease, radical treatment is to be considered only in patients with life expectancy of more than 20 years. Active surveillance has become the dominant management for low-risk prostate cancer, with the highest rates yet reported and almost complete uptake for very-low-risk cancer. Considering the excellent prognosis for this group and the uncertainties regarding Tookad VTP long term safety and implications for radical treatment, Tookad use is restricted to higher risk patients. Considering the above and the SAG discussion, the indication was revised to exclude very low risk disease. Bilateral treatment was also excluded from the indication, due to concerns regarding efficacy and safety (lower coverage of the treatment area, higher extraprostatic necrosis).

The safety evaluation subgroup analyses showed that the incidences of AEs and SAEs related to drug, device, or VTP procedure are similar in the indication population and the overall trial population. Regarding the special AEs (incontinence, erectile dysfunction, urinary symptoms) that occurred in at least 5% of the subjects in the indication population, the results are very similar to the overall trial population.

The level of acute and chronic morbidity in terms of erectile, bladder and bowel dysfunction in comparison to modern radical treatment techniques (e.g. nerve sparing prostatectomy/ robotic surgery/ intensity modulated radiotherapy) and other local treatments (e.g. cryotherapy) has been discussed. The Applicant has provided an analysis of time with toxicity up to 48 months, using data available to date from the 5-year follow-up study. Overall, a significantly lower time with erectile dysfunction and urinary incontinence was observed for the Tookad arm in the overall population. The reduction in time with toxicity in the indication population was comparable to the overall trial population. In a further analysis without imputation of post-radical therapy toxicities, the ratio for ED toxicities tends to improve significantly over time, which confirms the previous observation that ED toxicities arise earlier in the Tookad arm, but with a greater proportion of transient toxicities, whereas the onset is later in the Active Surveillance arm, but with more permanent toxicities. The absence of post-radical therapy imputations favours the Active Surveillance arm significantly. This analysis is limited by the fact that the underlying data failed to comprehensively capture toxicities after radical-therapies. A large post-authorisation study, PAES CLIN1501 PCM401, will provide relevant data to directly and robustly assess the time with genitourinary toxicities (see RMP).

There are no data on long term safety of Tookad VTP and the impact of the chronic effects of tissue necrosis is not known, particularly with regards to erectile dysfunction, bladder and bowel function but also in terms of impact on the ability to perform subsequent radical therapy (surgery or radiotherapy) and on its outcomes (see also discussion on clinical efficacy and pharmacology).

A review of 19 radical prostatectomy cases post-Tookad has shown that RT was significantly easier to perform and more effective (based on absence of positive margins) among patients who received unilateral VTP treatment compared to bilateral treatment. Hence, the exclusion of bilateral disease patients and the restriction to a single VTP procedure per patient in the indication sub-population results in a further reduction of risk.

Radical radiotherapy works through generation of free radicals to cause DNA damage and a hypoxic tumour environment, as would occur post Tookad -VTP induced vasoconstriction, is known to be more resistant to radiation damage. It could be hypothesized that incomplete vessel occlusion post VTP could lead to the selection of cancer cell lines that are more resistant to hypoxia, making further VTP treatments ineffective. The results of retreatments by Tookad of lobes previously treated by VTP, in terms of negative biopsies are not in favour of this hypothesis.

Unlike radiotherapy, Tookad D VTP therapy is not directed at DNA but it is questionable if free radicals and oxygen species that are generated could be detrimental if the tissue survives. A systematic review of all the positive cores taken in a prostate lobe that had previously been treated by Tookad VTP was performed by a board certified uropathologist with a specific expertise in prostate cancer. This review did not show any sign of more aggressive residual or recurrent tumours in the treated areas (data not shown).

Overall, it is uncertain whether Tookad VTP adversely influences the ability to later undertake radical therapy, either 'missed opportunity' through disease progression or due to the PD effect of vascular occlusion. Although the limited available data does not indicate greater difficulty to perform radical prostatectomy, further information should be collected in this regard.

Long term safety is included as missing information in the RMP. A seven-year follow-up extension (study PCM301, PAES) and a long-term observational cohort study (CLIN1501 PCM401, PAES) are expected to gather additional long term safety information on Tookad in patients with low risk prostate cancer.

"Induction of more aggressive tumour histology by Tookad VTP treatment" and "Difficulty of subsequent surgery due to reduced size and fibrosis of the VTP-treated prostate" are also included in the RMP as important potential risk. These potential risks will be monitored in the follow-up of PCM301 and in the above mentioned study CLIN1501 PCM401 as described in the RMP.

The SmPC contains relevant information to reflect the risks and uncertainties regarding the medium to long term outcome following Tookad VTP treatment, in particular in section 4.4 and section 4.8 but also in section 5.1 of the SmPC in which the effect on urinary morbidity (IPSS) and erectile function (IIEF) following Tookad have been included. Furthermore, information on potential benefits, risks and uncertainties will also be communicated to patients through the patient information guide and package leaflet, in order that they may take informed decisions regarding their therapeutic options. The Physician guideline will also contain information about approaches (including VTP with Tookad) for the treatment of prostate cancer and the potential benefits, risks and uncertainties of VTP with Tookad allowing an informed decision before deciding on treatment.

Regarding laboratory findings, there was no consistent difference between 2 groups except all subjects in the VTP arm had an elevated D-dimer (up to 20 x ULN) on the day after the VTP procedure. D dimer can be elevated post-surgery and also with inflammation so the elevation is likely related to the procedure. Only one case of hepatotoxicity was reported. Mild LFT abnormalities were recorded with 15.2% of patients shifting from Grade 0 ALT at Baseline to Grade 1 at Day 7 post-procedure. Hepatotoxicity and Alanine aminotransferase increased and aspartate aminotransferase increased are included in the SmPC (see section 4.8).

As Tookad is only administered in a surgical setting under medical supervision, the risk of overdose is limited. In addition, Tookad is only conditioned in vials of 200 and 400 mg, which further limits the risk. Overall, there is limited clinical information on overdose involving Tookad. Healthy subjects have been exposed to doses up to 15 mg/kg of padeliporfin di potassium (corresponding to 13.73 mg/kg of padeliporfin) without light activation and 23 patients have been treated with 6 mg/kg of padeliporfin di potassium (corresponding to 5.49 mg/kg of padeliporfin) without significant safety issues. However, a prolongation of photosensitisation is possible and precautions against light exposure should be maintained for an additional 24 hours. An overdose of the laser light may increase the risk of undesirable extraprostatic necrosis (see SmPC sections 4.4 and 4.9).

It is unknown if there is a systemic risk of vascular occlusion events in patients previously treated with systemic vascular endothelial growth factor (VEGF) or VEGF receptor antagonists or in those with an underlying increased risk of clot formation (e.g. autoimmune diseases). Concerning the prostate only, any increased vascular occlusion within the prostate lobe should be beneficial in terms of local treatment outcome.

Patients with abnormal clotting may develop excessive bleeding due to the insertion of the needles required to position the light fibres. This may also cause bruising, haematuria and/or local pain. It is not expected that a delay in clotting will reduce the effectiveness of the Tookad VTP treatment; however, it is recommended that drugs that affect clotting are stopped prior to and for the immediate period following the VTP procedure (see SmPC sections 4.4 and 4.5). The increased risk of bleeding in patients with clotting disorders if multiple needles are being inserted into the perineum is reflected in the important potential risk “Procedural related injuries and complications” and in the missing information “Use in patients with clotting disorders and concomitant use of anticoagulants or anti-platelet therapy”.

Anticoagulant medicinal products and those that decrease platelet aggregation (e.g. acetylsalicylic acid) should be stopped at least 10 days before the procedure with Tookad. Medicinal products that prevent or reduce platelet aggregation should not be started for at least 3 days after the procedure (see SmPC section 4.2).

Various aetiologies can lead to enteric fistula formation, many fistulas occur in the postoperative setting. Approximately 20 to 30 percent of all enterocutaneous fistulas arise in the setting of Crohn disease (spontaneous, following bowel resection). There is a concern that extra-prostatic necrosis in the setting of chronic pelvic inflammation, as in rectal inflammatory bowel disease, may increase the risk of recto-urethral fistula. Tookad VTP should only be administered, after careful clinical evaluation, to patients with a history of active rectal inflammatory bowel disease or any condition that may increase the risk of recto urethral fistula formation (see SmPC section 4.4). Current exacerbation of rectal inflammatory bowel disease is a contraindication (see SmPC section 4.3). Use in patients with inflammatory bowel disease is included under missing information in the RMP.

Data were reviewed according to age (≤65 versus >65 years of age) as well as for those patients with co-existing hypertension or diabetes. There was no signal of differential related safety other than would be expected from the patient age or co-morbidity with regard to the use of Tookad, the device or the overall procedure. The majority of those AEs are local-regional events due to the insertion of then needle and the swelling of the prostate which are not likely to be influenced by the age of the patient. The age groups over 75 years are under-represented but this reflects the product indication and the target population.

There is a relatively little experience on the use of Tookad in non-Caucasian and non- Hispanic patients. However, given the mechanism of action of the drug and the fact that no alteration for the procedure would be expected no differences in the safety profile between the mainly Caucasian population and others is anticipated.

There is no data available in patients with hepatic impairment. Biliary excretion is the major route of elimination of the drug. Therefore, exposure to padeliporfin is expected to be increased and/or prolonged in patients with biliary excretion impairment or cholestasis. The lack of data regarding hepatic impairment is recognized as missing information (see RMP). Tookad is contraindicated in patients who have been diagnosed with cholestasis (see SmPC section 4.3).

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 is also contraindicated (see SmPC section 4.3).

Tookad has no influence on the ability to drive or use machines. However, as the procedure includes general anaesthesia, patients should not perform complex tasks like driving or using machines until 24 hours after a general anaesthetic is employed (see SmPC section 4.7).

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

Additional expert consultations

See discussion on clinical efficacy.

2.6.2. Conclusions on the clinical safety

The safety profile of Tookad VTP has been adequately characterised in the short term and achievement of a clinically relevant delay in important toxicities has been shown based on analysis of time with toxicity up to 48 months, using data available to date from the 5-year follow-up study.

Adequate recommendations to manage the risks have been included in the SmPC. Furthermore additional risk minimisation measures are in place to ensure adequate information to the patients for an informed decision. There are uncertainties about the long term safety of Tookad VTP that will be adequately addressed post authorisation with a number of post-authorisation studies (see RMP and Annex II).

The CHMP considers the following measures necessary to address issues related to safety:

Post-authorisation efficacy study (PAES): In order to further investigate long-term efficacy of Tookad and its impact on disease progression including potential impact on the efficacy of subsequent radical therapy in patients with low risk prostate cancer as well as further characterise the long term safety of Tookad, the MAH should submit the results of a randomised phase 3 study in patients with localised prostate cancer compared to active surveillance (7-year follow-up study including in an depth biopsy study) (PCM301 FU5). Submission of final study results: 31/12/2020.

Post-authorisation efficacy study (PAES): In order to further investigate long-term efficacy of Tookad and its impact on disease progression including potential impact on the efficacy of subsequent radical therapy in patients with low risk prostate cancer (excluding very low risk) as well as further characterise the long term safety of Tookad, the MAH should conduct and submit the results of a long-term observational cohort study of patients with unilateral low risk localised prostate cancer treated with Tookad VTP (CLIN1501 PCM401). Submission of final study results: 31/12/2025.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• Photosensitivity • Urethral stenosis
Important potential risks	• Complications of extra-prostatic necrosis • Procedural related injuries and complications • Long-term erectile dysfunction (>6 months) • Long-term urinary incontinence (>6 months) • Procedural related injuries and complications due to non-compliance with the device manufacturers' instructions and recommended guidance for the VTP procedure • Induction of more aggressive tumour histology by TOOKAD VTP • Difficulty of subsequent radical therapy due to reduced size and fibrosis of the VTP-treated prostate
Missing information	• Use in patients with inflammatory bowel disease • Use in patients with hepatic impairment • Use in patients with clotting disorders and concomitant use of anticoagulants or anti-platelet therapy • Long-term safety

Pharmacovigilance plan

Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PCM301 FU5 (Addendum 1 to CLIN1001 PCM301). A European Randomised Phase 3 Study to Assess the Efficacy and Safety of TOOKAD® Soluble for Localised Prostate Cancer Compared to Active Surveillance. Post Study 5-year Follow-up. Clinical, category 1 (PAES)	To collect follow-up data of the CLIN1001 PCM301 randomized trial of TOOKAD® Soluble Focal Treatment versus Active Surveillance for Localised Prostate Cancer over an additional 60 months follow-up for a total of 84 months (7 years) follow-up from the initial randomisation. To also collect long-term follow-up of study PCM301 with regard to incidence of curative treatment and metastatic disease in both arms. In addition, overall and prostate cancer specific survival will be assessed.	- → Long-term urinary incontinence (>6 months) - → Long-term erectile dysfunction - → Urethral stenosis - → Complications of extra-prostatic necrosis - → Induction of more aggressive tumour histology - → Difficulty of subsequent radical therapy due to reduced size and fibrosis of the VTP-treated prostate	Started	Final report Q4 2020
Addendum to PCM301FU5 In-depth biopsy study of the post study 5-year follow-up of the	The principal objective of this In-Depth Biopsy Study is to measure cancer progression through biopsies in patients who were enrolled in the CLIN1001 PCM301 randomized trial of TOOKAD® Focal Treatment versus Active	This will address the safety concern of whether VTP leads to the induction of more aggressive tumour histology	Planned (anticipated start: Q1 2018)	Final report Q4 2020

European randomised phase 3 study to assess the efficacy and safety of TOOKAD® Soluble for localised prostate cancer compared to active surveillance Clinical, category 1 (PAES)	Surveillance for Localised Prostate Cancer. The study will also record information on conditions and feasibility of radical therapy when available			
CLIN1501 PCM401 A Long-term Observational Cohort Study of Patients with Unilateral Low Risk Localised Prostate Cancer Treated with TOOKAD® Vascular Targeted Photodynamic Therapy in Current Clinical Practice Clinical, Category 1 (PAES)	**Primary objectives:** The co-primary objectives of the study are to assess the long term (7 years) safety and effectiveness of TOOKAD® VTP in the real life clinical practice. **Specific co-primary objectives:** - To quantify the time with toxicities associated with TOOKAD® VTP and with potential subsequent radical therapy (radical prostatectomy, radiotherapy, others) received by patients on the long term (7 years). Toxicities considered for this analysis are erectile dysfunction and urinary incontinence [toxicities considered in the pivotal benefit/risk assessment] - To assess the progression of disease over time in patients treated with TOOKAD® VTP and the use of radical therapy associated with these progressions **Secondary Objectives:** - To quantify the incidence of identified and potential risks specified in the Risk Management Plan (RMP)	- Procedural related injuries and complications - Long-term erectile dysfunction (>6 months) - Urinary incontinence, including long-term (> 6 months) - Complications of extra-prostatic necrosis - Urethral stenosis - Photosensitivity - Effectiveness of Risk Minimisation Measures	Planned (anticipated start mid-2018)	Interim report Q2 2022 Final report approx. Q4-2025

	in·patients·treated·with·TOOKAD®·VTP:··¶ --→ Procedural·related·injuries·and·complications·¶ --→ Long-term·urinary·incontinence·(>·6·months)¶ --→ Complications·of·extra-prostatic·necrosis¶ --→ Erectile·Dysfunction·(transient·and·long·term)¶ --→ Urethral·stenosis¶ --→ Photosensitivity¶ --→ To·quantify·separately·the·time·with·erectile·dysfunction·toxicity·and·urinary·incontinence·toxicity,·including·these·toxicities·after·radical·therapy¶ --→ To·assess·the·effectiveness·of·risk·management·measures·(RMM):¶ --→ Incidence·and·timing·of·photosensitivity·(during·hospital·stay,·after·hospital·discharge)¶ --→ ·Frequency·of·reports·of·procedural·related·injuries·and·complications·¶ --→ To·assess·the·aggressiveness·of·cancer·in·patients·progressing·after·TOOKAD®·VTP¶ --→ To·assess·the·feasibility·and·difficulty·of·radical·treatment·in·progressing·patients·and·their·results¶ --→ To·assess·the·proportion·of·patients·free·of·disease·¶ --→ To·assess·the·adherence·of·physicians·to·VTP·treatment·guidance·and·the·reliability·of·the·Patient·Management·Algorithm·¶ --→ To·assess·the·prostate·cancer·specific·mortality·of·patients·treated·with·TOOKAD®·VTP·over·7·years·and·survival·over·10·years.¶			

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Photosensitivity	SmPC sections 4.4, 4.8 and 5.3 Prescription only medicine Restricted to hospital use Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure	**In the Guideline for Physician:** Guidance for light protection for the patient is provided in Section 3. **Patient Information Guide** To allow the patients to make an informed choice as to whether VTP is the right option for them given that they may get a photosensitivity reaction. The patients will be asked to sign a receipt form stating that they have received the guide and that they have had their treatment options explained to them
Urethral stenosis	SmPC sections 4.4 and 4.8 Prescription only medicine Restricted to hospital use Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure	None
Complications of extra-prostatic necrosis	SmPC sections 4.4 and 4.8 Prescription only medicine Restricted to hospital use Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure	None
Procedural related injuries and complications	SmPC sections 4.4, 4.5 and 4.8 Prescription only medicine Restricted to hospital use Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Long-term erectile dysfunction (>6 months)	SmPC section 4.8 Prescription only medicine Restricted to hospital use Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure	None
Long-term urinary incontinence (>6 months)	SmPC sections 4.3 and 4.8 Prescription only medicine Restricted to hospital use Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure	None
Procedural related injuries and complications due to non-compliance with the device manufacturers' instructions and recommended guidance for the VTP procedure	SmPC sections 4.2 and 4.4 Prescription only medicine. Restricted to hospital use. Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure.	None
Induction of more aggressive tumour histology by TOOKAD VTP	Biopsies reviewed by trained pathology personnel Restricted to hospital use Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure	None
Difficulty of subsequent radical therapy due to reduced size and fibrosis of the VTP-treated prostate	Restricted to hospital use Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.7, dated 14th September, is acceptable.

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 declared that padeliporfin has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers padeliporfin to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

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, Tookad (padeliporfin) 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

The indication of Tookad applied by the applicant is for the treatment of adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and:

- Clinical stage T1c or T2a,
- Gleason Score ≤ 6, based on high-resolution biopsy strategies,
- PSA ≤ 10 ng/mL,
- 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1 -2 positive cancer cores with ≥ 50 % cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/cm^3.

3.1.2. Available therapies and unmet medical need

The recommended options for patients with low risk localised prostate cancer are active surveillance or radical treatment (prostatectomy or radiotherapy). Studies have shown that for any of these options the case specific survival at 10 years was very high. Despite the low risk, progression is observed among patients on active surveillance. Studies have defined progression either in terms of increase of the risk level or decision to move to radical treatment. In this patient group, survival rate is not a differentiating criterion for the choice of treatment and one has to rely on other criteria such as reduction of progression and preservation of quality of life to differentiate the relative benefits of the different treatment options. Focal ablative therapies as cryotherapy and high intensity focused ultrasound (HIFU) are recommended in European guidelines only as alternative therapeutic options for low risk patients who are unfit for surgery or radiotherapy. The aim of focal treatment is to delay radical therapy or avoid unnecessary radical therapy thereby avoiding its toxicities.

3.1.3. Main clinical studies

The main evidence of efficacy is a multicentre, randomized, open label Phase 3 study in Europe (Study CLIN1001 PCM301) comparing the effect of the Tookad VTP procedure versus active surveillance in men with previously untreated low-risk localised prostate cancer.

3.2. Favourable effects

In patients with low risk prostate cancer Tookad VTP produced a statistically significant improvement in the probability of a negative biopsy at 24 months (49% vs. 13.5%, RR=3.62) compared to active surveillance (periodic monitoring of known prostate cancer). Results were consistent in the mITT and PP populations and on subgroup analysis of unilateral (RR 3.48 [2.30, 5.24]) and bilateral (4.31 [1.80, 10.32]) disease. Sensitivity analysis showed no effect of age, number of positive cores, prostate volume and baseline disease status (unilateral/ bilateral) on the outcome (risk ratio in ITT population at 24 months = 3.67 [2.53, 5.33]). In just the treated lobe the proportion of patients with negative biopsies at 24 months was 62.6%.

A post-hoc sensitivity analysis that assumed missing biopsies due to radical therapy to be negative still favoured Tookad, although the effect size was smaller (54.9% vs. 40.1%, RR 1.37 [1.11, 1.68] p=0.003). The median time to progression based on any one of a list of pre-specified events (>3 cores definitively positive for cancer; Gleason primary or secondary pattern ≥4; ≥1 cancer core length > 5 mm; PSA > 10 ng/mL in 3 consecutive measures; T3 prostate cancer; metastasis; prostate cancer-related death) was twice as long in the Tookad as the active surveillance group (28.3 vs. 14.1 months, p<0.001). The proportion of subjects who progressed over 24 months in the Tookad group was lower than in the active surveillance group (28.2% vs. 58.5%; HR=0.34 [0.25; 0.47]).

No significant effect of covariates [baseline age, number of cores positive, prostate volume and disease status (unilateral/bilateral)] was observed. Occurrence of each individual criterion for progression was reduced by Tookad. The results appeared robust in the different populations (mITT and PP), according to baseline disease status (uni/ bilateral) and the sensitivity analysis that assumed that all patients who withdrew or opted for radical therapy were treatment failures (progression 35.9% vs 69.1%; HR = 0.38 [0.28, 0.50]).

By 24 months, 12 (5.8%) subjects in the Tookad VTP group compared to 60 (29.0%) in the active surveillance group had undergone radical therapy. The median time to radical therapy was 27 months in the active surveillance arm and not reached in the Tookad arm, a statically significant difference (p<0.001).

The applicant proposed a revised indication for the treatment of unilateral low risk localised prostate cancer in adult men with a life expectancy ≥ 10 years (excluding very low risk patients). The population targeted by the indication represents 38% of the overall trial population with a good balance of the Tookad arm (80 patients, 39% of overall trial population) and the Active Surveillance arm (78 patients, 38% of overall trial population).

The risk ratio for negative biopsy at M24 was greater in the indication sub-population than in the overall population when considering either only the lobe diagnosed at baseline (RR=4.61 vs. 3.24) or the whole gland (RR=4.39 vs. 3.62)

The hazard ratio for disease progression over 24 months was improved in the indication sub-population compared to the overall population when considering either only the lobe diagnosed at baseline (HR=0.11 vs. 0.17) or the whole gland (RR=0.31 vs. 0.34).

The absolute reduction in risk of receiving radical therapy was greater in the indication sub-population than in the overall population: 31% vs. 26% at M24 (based on full study data) and 29% vs. 25% at M48 (based on preliminary follow-up data among ~62% of patients)

The reduction of time with genitourinary toxicity was increased in the indication sub-population compared to the overall population over 24 months and almost equivalent over 48 months, with:

- A ratio of 0.85 vs. 0.93 over 24 months for overall time with genitourinary toxicities (erectile dysfunction: 1.07 vs. 1.15; urinary incontinence: 0.17 vs. 0.23), with statistical significance only for urinary incontinence;
- A ratio of 0.62 vs. 0.58 over 48 months (preliminary follow-up data) for overall time with genitourinary toxicities (erectile dysfunction: 0.68 vs. 0.63; urinary incontinence: 0.37 vs. 0.36), with statistical significance.

3.3. Uncertainties and limitations about favourable effects

Follow-up time within the study was not sufficient to reliably estimate the median progression-free survival. Beyond 2 years the efficacy of Tookad VTP is assessed clinically, with uncertain input from the absolute PSA value and no prostate biopsies. Therefore, the additional analysis provided on delay to progression and risk of/time to receiving radical therapy should be considered with caution considering these limitations.

Nevertheless, proportions of patients with no disease progression in the initially treated lobe were substantially higher in the Tookad than in Active Surveillance arm, with 95% vs. 55% of patients without ipsilateral disease progression at M15 respectively and 90% vs. 42% at M27. When considering the whole gland, the proportions for absence of progression were lower with 73% and 36% at M15 for Tookad and Active Surveillance respectively and 64% and 25% at M27. This analysis confirmed the significant reduction in progression of disease and need for radical therapy, as reported previously based on the review of hazard ratios in Kaplan-Meier analyses. This preliminary assessment of longer term benefits has to be taken with caution and will have to be confirmed in the two PAES studies that will be conducted, study PCM301 FU5 and study CLIN1501 PCM401. Furthermore, an in-depth biopsy sub-study as part of study PCM301 FU5 is expected to provide relevant data beyond 24 months.

With regards to benefits in terms of reduction of time with toxicity (see also under unfavourable effects below), the assessment of time with toxicity was not included as a specific endpoint in the initial study design it was not collected after RT. Based on an approach imputing to these patients the toxicity profile reported in Study ProtecT post-radical prostatectomy, Tookad led to a positive benefit. However there remain some uncertainties due to the imputations. Two large PAES studies will provide relevant data on time with genitourinary toxicities to alleviate this uncertainty.

3.4. Unfavourable effects

When given alone, as in the healthy volunteer study, Tookad is very well tolerated. However, there is a risk of phototoxicity and, as a result, precautions against exposure to light during the procedure and for a short time afterward is necessary. The half-life of Tookad ranges from 1.14-1.70 hours in prostate cancer patients and so, unlike other photosensitising agents, these precautions do not have to be in place for more than 48 hours and this duration provides a very conservative approach given the very short half-life.

The majority of adverse events were procedure related due insertion of the optical fibres through the perineum and light activation of Tookad causing necrosis. The most common all cause adverse events in the 398 patients treated with the recommended dose of Tookad / light energy across the prostate clinical studies were genitourinary, including dysuria (28.4%), erectile dysfunction (25.6%), haematuria (20.6%), perineal pain (15.6%) and urinary retention (14.1%). Most events were low grade and resolved in a few days without sequelae. About 7% were considered Grade 3 at the recommended dose and light intensity, again genitourinary [dysuria (1.3%), haematuria (0.5%), urinary retention (1.0%), prostatitis (0.8%), erectile dysfunction (0.8%) and a Grade 3 prostatic abscess].

There is the additional risk inherent in undergoing a general anaesthetic and there were rare reports of bronchospasm, hypersensitivity and ECG changes. Also device related failures were reported, resulting in treatment cancellation or defective calibration of the optical light meter and extra-prostatic necrosis.

Serious TEAEs were reported in 19.8% of patients across the studies under the recommended treatment conditions, again mainly genitourinary disorders. These included urinary retention, urethral stenosis, haematuria, dysuria, prostatitis, urinary tract infection and orchitis.

TURP has been added to the list of contraindications for treatment with Tookad (see SmPC section 4.3) since one such patient experienced total urinary incontinence, necessitating insertion of an artificial urinary sphincter.

Prostatic symptoms according to the IPSS transiently worsened but were equal or better than baseline by 6 months. Erectile function (IIEF-15 scores) showed transient and moderate worsening up to 3 months after the procedure that persisted to 12 months but the result at 24 months was comparable to AS. This was due to patients in the AS arm undergoing radical therapy.

Analysis of time with toxicity up to 48 months, using data available to date from the 5-year follow-up study were provided. Acknowledging the limitations of this analysis, significantly lower time with erectile dysfunction and urinary incontinence was shown for the Tookad arm in the overall population. The estimated relative time with toxicity for Tookad vs. AS overall ratio was 0.93 (95% CI= 0.47-1.03); 1.15 (95% CI= 0.47-1.03) for erectile dysfunction and 0.23 (95% CI= 0.13-0.45) for Urinary Incontinence. The ratio of relative time with toxicity in the overall trial population is greater at M48 compared to M24: 0.58 overall (95% CI: 0.27-0.64), with 0.63 for ED (95% CI: 0.28-0.69) and 0.36 for UI (95% CI: 0.16-0.47). The overall toxicity is slightly reduced and the ED toxicity is slightly increased at M24, but without a statistically significant difference. The UI toxicity is substantially reduced with a statistically significant difference. The reduction in time with toxicity in the indication population was comparable to the overall trial population.

In a further analysis without imputation of post-radical therapy toxicities, the overall ratio of time with genitourinary toxicities for Tookad vs. Active Surveillance is 2.77 over 24 months and 1.46 over 48 months. These results are largely driven by the time with ED toxicity, which is the most prevalent. The ratios for time with ED toxicities are 3.85 at M24 and 1.40 at M48, while the ratios for time with UI toxicities are 0.13 at M24 and 2.39 at M48.

The safety profile in the final restricted indication was comparable to that of the overall study population.

3.5. Uncertainties and limitations about unfavourable effects

Long-term follow-up for safety is missing, including the local effect of extra-prostatic necrosis. It remains to be seen if later cases of fistula, incontinence or urethral stenosis occur. It is unclear if urinary morbidity will be worse in patients with greater baseline voiding difficulties including a history of urinary retention or benign prostatic hypertrophy (BPH).

It is also uncertain whether Tookad VTP adversely influences the ability to later undertake radical therapy, either 'missed opportunity' through disease progression or due to the PD effect of vascular occlusion. There is a concern that associated fibrosis may make surgery more difficult and impair post-operative wound healing although the limited available data does not indicate greater difficulty to perform radical prostatectomy.

The risk of more difficult radical prostatectomy has been reported in patients who received bilateral VTP (in particular nerve sparing radical prostatectomy). By restricting the target indication to patients with unilateral disease and a single VTP procedure, this risk has been reduced.

Although no increase in the risk of metastasis or prostate cancer-related mortality has been detected to date based on the Phase II and Phase III follow-up data available to date, additional data will be collected in the continued follow-up of PCM301 (PCM301 FU5) and the PAES CLIN1501 PCM401 study to further confirm the absence of a meaningful risk.

Overall, the uncertainties about the long term safety of Tookad VTP will be adequately addressed post authorisation with a number of post-authorisation studies (see RMP and Annex II).

3.6. Effects Table

Table 73 Effects Table for Tookad (padeliporfin) for treatment of low risk localised prostate cancer (study PCM 301 efficacy data cut-off: December 2015)

Effect	Short Description	Unit	Treatment VTP	Control AS	Uncertainties / Strength of evidence
Negative biopsy month 24	Absence of definite cancer at 24 months	%	49.0%	13.5%	Risk ratio 3.62 (95% CI: 2.50, 5.26; *P*: <0.001) Median TTP: 28.3 months v. 14.1 months
Initiation of radical therapy	Percentage of subjects who initiated radical therapy by 24 months (95% CI)	%	6.2 (3.6, 10.7)	30.8 (24.8, 38.0)	
Serious adverse drug reactions (Grade 3)	NCI Common Terminology Criteria for Adverse Events	%	7%	N/A	Dysuria (1.3%), haematuria (0.5%) urinary retention (1%), prostatitis (0.8%) erectile dysfunction (0.8%) and 1 prostatic abscess; Additional important risks identified: Skin photosensitivity; Transient urinary symptoms; Urinary tract infection; Prostatitis; Perineal pain/haematoma; Erectile dysfunction
Life-threatening (Grade 4) or fatal adverse drug reactions (Grade 5)	NCI Common Terminology Criteria for Adverse Events	No.	2	N/A	At the recommended dose and light intensity in 398 patients: bronchospasm related to the anaesthetic (G4); myocardial infarction (G5)

Abbreviations: VTP, vascular targeted therapy; AS; active surveillance; TTP, time to progression; N/A, not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Beneficial effects for Tookad VTP in low risk prostate cancer have been shown in terms of an increased number of patients with negative biopsies at 2 years and longer median time to disease progression in comparison to monitoring patients with known disease. These are results that are robust and maintained in sensitivity analyses, including adjustment for baseline age, number of positive cores, prostate volume and disease status (unilateral/ bilateral).

The positive benefits described in the overall trial population are confirmed in the target indication sub-population with significant statistical significance. Importantly, this was shown for each of the benefits relevant to the assessment of minimally invasive cancer treatments (EMA/CHMP/703715/2012 Rev. 2 – Dec 2015), namely: absence of positive biopsy, reduction in progression of disease/need for radical therapy, reduction in risk of radical therapy, and reduction in time with genitourinary toxicities. Furthermore, sub-group analyses have shown that benefits of Tookad vs. Active Surveillance are maximized in the final restricted indication.

Overall, Tookad VTP was shown to deferring progression by median difference of about 14 months compared to active surveillance which is considered clinical relevant in the selected patient population of patients with low risk prostate cancer (excluding very low risk) wishing to defer radical therapy being fully informed about potential risks and uncertainties. The estimated risk of/time to receiving radical therapy (RT), with its consequent ADRs, has been shown to be substantially delayed although these analyses have some limitations and should be considered with caution.

Adverse events from Tookad –VTP are mainly local genito-urinary effects. These occurred at a higher frequency with VTP compared to AS (e.g. haematuria 28.4 vs. 2.9%; dysuria 27.4 vs. 2.4%, ejaculation failure 8.1% vs. 0.5%, erectile dysfunction 37.6% vs. 11.6%). The frequency and severity of long term erectile dysfunction post Tookad-VTP remains unclear. An analysis of time with toxicity to 48 months, using data available to date from the 5-year follow-up study showed a significantly lower time with erectile dysfunction and urinary incontinence for the Tookad arm, probably due to RT avoidance (with the associated uncertainties around the decision to proceed with RT).

The proportion of patients experiencing AEs with Tookad is within the range of incidence observed with radical prostate cancer therapies. Retaining potency is a strong motivator for patients to avoid radical treatment.

To address the remaining uncertainties about the long term efficacy and safety of Tookad VTP, two PAES will be conducted. The two studies, follow-up of PCM301 (PCM301 FU5) and PAES CLIN1501 PCM401, will further investigate long-term efficacy of Tookad and its impact on disease progression including potential impact on the efficacy of subsequent radical therapy as well as further characterise the long term safety of Tookad.

Furthermore the product information and patient and physicians guides will adequately inform about the risks and uncertainties of Tookad VTP to allow an informed decision before deciding on starting treatment.

3.7.2. Balance of benefits and risks

The increased number of patients with negative biopsies at 2 years and the longer median time to disease progression observed with Tookad in comparison to monitoring patients with known disease are relevant short-term benefits. Furthermore, considering the toxicity of radical therapy, delaying radical therapy by median difference of about 14 months compared to active surveillance is considered relevant in patients with low risk prostate cancer (excluding very low risk) wishing to defer radical therapy being fully informed about potential risks and uncertainties. The uncertainties about long term are considered acceptable given the measures in place to adequately inform both physicians and patients and the post authorisation studies to be performed.

Based on data available to date, the restricted use of Tookad in the target indication sub-population (unilateral low-risk excluding very low-risk disease), with limitation to a single procedure enables to maximize the positive benefits of the treatment, while minimizing the risk of compromising salvage radical therapy. Although still preliminary and somewhat uncertain, the longer-term data available to date points to maintenance of the benefits with no signal of increased risk.

Overall, the benefits of Tookad VTP are considered to outweigh the risks in patients with unilateral disease and low risk prostate cancer Tookad (excluding very low risk) as defined in section 4.1 of the SmPC.

3.7.3. Additional considerations on the benefit-risk balance

There is insufficient information on retreatment of the ipsilateral lobe or sequential treatment of the contralateral lobe to determine the efficacy and safety of a second Tookad VTP procedure. Therefore, retreatment of the same lobe or sequential treatment of the contralateral lobe of the prostate are not recommended (see sections 4.2 and 4.4).

3.8. Conclusions

The overall B/R of Tookad is positive.

The divergent position is appended to this report.

4. Recommendations

Outcome

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

Tookad is indicated as monotherapy for adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and:

- Clinical stage T1c or T2a,
- Gleason Score ≤ 6, based on high-resolution biopsy strategies,
- PSA ≤ 10 ng/mL,
- 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1 -2 positive cancer cores with ≥ 50 % cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/cm^3.

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

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

Risk Management Plan (RMP)

The 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 Tookad in each Member State the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness and providing information concerning the signs and symptoms of certain important identified risks of padeliporfin, including photosensitivity, and also information on the existing therapeutic approaches (including VTP with Tookad) for the treatment of the type of prostate cancer, potential benefits, risks and uncertainties of VTP with Tookad .

The MAH shall ensure that in each Member State where Tookad is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Tookad have access to/are provided with the following educational package:

- Patient information guide
- Physician guideline

The Patient information guide about Tookad should contain the following key elements:

- Information on the existing therapeutic approaches (including VTP with Tookad) for the treatment of the type of prostate cancer
- Information on the potential benefits, risks and uncertainties of VTP with Tookad, including: uncertainties on long-lasting benefit of Tookad; uncertainties on long-term safety of Tookad and efficacy/safety of any further treatments required such as radical prostatectomy
- Information on adverse drug reactions and the likelihood of them getting them, including: erectile dysfunction, urinary incontinence, urinary retention/urethral stricture, and photosensitivity and the need to follow the rules to protect themselves against the light after the procedure for 48 hours.

The Physician guideline about Tookad should contain the following key elements:

- The approaches (including VTP with Tookad) for the treatment of his prostate cancer and the potential benefits, risks and uncertainties of VTP with Tookad:

- To state that information beyond two years after the Tookad -VTP procedure is limited and consequently, data on the long-term efficacy and safety of Tookad -VTP are currently not available
- Information on the efficacy/safety of any subsequent treatments required, such as radical prostatectomy, is currently lacking

- Explain what the VTP procedure involves, including the need to follow the rules to protect the Patient against light after the procedure for 48 hours, due to the photosensitising effect of Tookad and provide a copy of the Tookad Package Leaflet to the Patient ahead of the VTP procedure
- Explain what side effects the Patient might expect and the likelihood of him getting them
- Explain the procedure as well as relevant efficacy and safety results of Tookad with simple graphics included in the Patient Information Guide.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further investigate long-term efficacy of TOOKAD and its impact on disease progression including potential impact on the efficacy of subsequent radical therapy in patients with low risk prostate cancer as well as further characterise the long term safety of TOOKAD, the MAH should submit the results of a randomised phase 3 study in patients with localised prostate cancer compared to active surveillance (7-year follow-up study including in an depth biopsy study) (PCM301 FU5).	Submission of final study results: 31/12/2020
Post-authorisation efficacy study (PAES): In order to further investigate long-term efficacy of TOOKAD and its impact on disease progression including potential impact on the efficacy of subsequent radical therapy in patients with low risk prostate cancer (excluding very low risk) as well as further characterise the long term safety of TOOKAD, the MAH should conduct and submit the results of a long-term observational cohort study of patients with unilateral low risk localised prostate cancer treated with TOOKAD VTP (CLIN1501 PCM401).	Submission of final study results: 31/12/2025

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 padeliporfin is considered to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

5. Appendix

1. Divergent position to the majority recommendation

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Tookad.

The reasons for divergent opinion were as follows:

Based on the currently available data the benefit-risk balance for Tookad is considered to remain undetermined. Major uncertainties exist regarding efficacy and safety:

- Although a short term benefit in terms of progression of the disease has been shown in study PCM301, the clinical relevance remains to be established. A delay in radical surgery as secondary endpoint was demonstrated, but clear criteria defining need for radical therapy were lacking (as required by EMA guideline, see appendix 4, EMA/CHMP/703715/2012 Rev. 2). Not all patients that progressed received radical treatment, meaning that the choice for radical therapy could have been biased by the open-label study design. This came at the expense of a relative high incidence of side effects, in particular erectile dysfunction.
- The current restricted indication population concerns a post hoc determined subgroup that was not identified a priori and replication of the results was not provided (as required by the relevant EMA draft guideline, see EMA/CHMP/539146/2013). The data also do not fulfil the criteria that are required for one pivotal study (Points to consider on application with meta-analyses or one pivotal study CPMP/EWP/2330/99).
- Follow-up data are inadequate. In the context of low-risk prostate cancer, with active surveillance being a valid therapeutic option and the existence of effective treatments in case of progression, it is the long-term benefits (and risks) that bear more weight in the overall benefit-risk assessment. Too limited data were collected in study PCM301 beyond 2 years, especially because prostate biopsies were not specified after that time point in the study protocol. As a consequence, the efficacy data are not sufficient to support at least non-inferiority in terms of long-term outcome and the long–term safety profile is unclear.
- Importantly, there is virtually no data on the potential consequences of post-Tookad local scarring in case of disease progression. Thus, the safety and efficacy of subsequent radical therapy is uncertain and it still needs to be demonstrated that treatment with Tookad does not compromise the eligibility for and the results of subsequent radical therapy. The existence of a small study assessing the feasibility of radical surgery following focal therapy is not sufficiently reassuring in this respect (Lebdai et al.).

In conclusion, although the efficacy and safety results in study PCM301 up to 2 years are noted, these are considered to be insufficient to compensate for the absence of an established long-term efficacy and safety benefit of Tookad. We cannot conclude on a positive (relative) B/R, given the existence of highly effective alternative therapy (radical therapy) and active surveillance as a valid alternative patient management option, and a risk of compromising long-term outcome is not considered justified. Until more is known, the application is considered not approvable.

London, 14 September 2017

CHMP Members expressing a divergent position:

Alexandre Moreau	14 September 2017	Signature: ……..
Johann Lodewijk Hillege	14 September 2017	Signature: ……..