STEBA BIOTECH S.A.

7 Place du Théâtre
L-2613 Luxembourg

CLINICAL TRIAL PROTOCOL

Study of the Efficacy, Safety and Quality of Life after TOOKAD® Soluble Vascular Targeted Photodynamic therapy (VTP) for Minimally Invasive Treatment of Localized Intermediate Risk Prostate Cancer.

Product: TOOKAD® Soluble

Study Code: CLIN1601 PCM204

Version: 6.0

Date: 1st October 2018

CONFIDENTIAL

1 GENERAL INFORMATION

STEBA BIOTECH S.A.

CLINICAL STUDY PROTOCOL

Study title:	Study of the Efficacy, Safety and Quality of Life after TOOKAD® Soluble Vascular Targeted Photodynamic therapy (VTP) for Minimally Invasive Treatment of Localized Intermediate Risk Prostate Cancer.
Study number:	**CLIN1601 PCM204**
Name of product:	TOOKAD® Soluble
Indication:	Prostate cancer
Sponsor:	Steba Biotech S.A.
	7 Place du Théâtre, L-2613 Luxembourg
Development phase:	Phase IIb
Protocol release date:	1st October 2018

This study will be conducted in accordance with Good Clinical Practice and in full compliance with the World Medical Association's Declaration of Helsinki, as amended.

Confidentiality Statement

1.1 Signatures

Signature Page for Sponsor

Bertrand Gaillac

International Medical Project Leader

Study title: Study of the Efficacy, Safety and Quality of Life after TOOKAD® Soluble Vascular Targeted Photodynamic therapy (VTP) for Minimally Invasive Treatment of Localized Intermediate Risk Prostate Cancer.

Study No: CLIN1601 PCM204

Protocol and date: Version 6.0 dated 1st October 2018

Protocol approved by the following:

Job Title	*Print Name*	*Signature*	*Date*
International Medical Project Leader	Dr Bertrand Gaillac		23 oct 2018

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Study title: Study of the Efficacy, Safety and Quality of Life after TOOKAD® Soluble Vascular Targeted Photodynamic therapy (VTP) for Minimally Invasive Treatment of Localized Intermediate Risk Prostate Cancer.

Study No: CLIN1601 PCM204

Protocol version and date: Version 6.0 dated 1st October 2018

I the undersigned have read this protocol and agree to conduct this study in accordance with all protocol stipulations, the Declaration of Helsinki and Good Clinical Practice.

Print Name	*Signature*	*Date*
Prof. Jonathan Coleman		15/10/18

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1.4 Synopsis

Name of Sponsor/Company**:** STEBA Biotech S.A.		
Name of Finished Product: TOOKAD® Soluble	Protocol No: **CLIN1601 PCM204**	For National Authority Use Only
Name of Active Ingredient: Padeliporfin/ Palladium Bacteriopheophorbide Monolysotaurine (WST11)	Volume:	

TITLE OF STUDY:

Study of the Efficacy, Safety and Quality of Life after TOOKAD® Soluble Vascular Targeted Photodynamic therapy (VTP) for Minimally Invasive Treatment of Localized Intermediate Risk Prostate Cancer.

STUDY CENTRE(S):

It is expected to involve one single center (Memorial Sloan-Kettering Cancer Center) in the United States of America.

DEVELOPMENT PHASE: This study is designed as a Phase IIb study

STUDY RATIONALE

Based on the positive phase II and phase III studies conducted in the United States, Europe, Canada and Latin America, it is expected that TOOKAD® Soluble VTP treatment as a partial gland ablation modality indicated for localized prostate cancer will result in a significant percentage of patients becoming cancer-free, with minimal change from baseline erectile and urinary function and with a good safety profile. These findings have thus far been consistent across the trials in low volume Gleason 3+3 prostate cancer, a disease considered to be low-risk. Among trial participants in the recently completed Phase III Latin American study (PCM304), where few patients with intermediate-risk Gleason score 3+4 cancer were treated, the results appear similar to those of treated men with Gleason 3+3 disease. Therefore, establishing the safety and efficacy of this procedure specifically in men with localized, intermediate risk prostate cancer is an important research objective to be addressed in this study. Interest in performing this study in the U.S. at a center of excellence will provide rigorous evaluation of the technique and oncologic outcomes as well as detailed study of functional metrics.

STUDY HYPOTHESIS

TOOKAD® Soluble Vascular Targeted Photodynamic therapy (VTP), as a partial gland ablation therapy for men with unilateral intermediate risk prostate cancer, will result in the absence of detectable, clinically significant prostate cancer in over 70% of treated men.

PRIMARY OBJECTIVE

To evaluate the absence of biopsy detectable Gleason grade 4 or 5 prostate cancer tumors anywhere in the prostate gland on 12-month, post-treatment biopsy following TOOKAD® Soluble-VTP in men with Gleason score 7 (3+4) prostate cancer.

SECONDARY OBJECTIVES

1. To describe the rate of responders, with response defined as the absence of any Gleason grade 4 or 5 biopsy on or before months 24, 36, 48 and 60. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of gleason grade 4 or 5, the subject will be considered to have responded;
2. To describe the rate of responders, with response defined as the absence of any prostate cancer on biopsy on or before months 3, 12, 24, 36, 48 and 60. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of any cancer, the subject will be considered to have responded;
3. To describe the rate of responders, with response defined as the absence of any Gleason grade 4 or 5 biopsy on or before months 12, 24, 36, 48 and 60 in the treated lobe. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of gleason grade 4 or 5, the subject will be considered to have responded;
4. To describe the rate of responders, with response defined as the absence of any prostate cancer on biopsy on or before months 3, 12, 24, 36, 48 and 60 in the treated lobe. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of any cancer, the subject will be considered to have responded;
5. To describe the change in biopsy results between 3 , 12, 24, 36, 48 and 60 months TOOKAD® Soluble-VTP;
6. To describe changes in urinary and erectile function and the potential impact on QOL using International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF) questionnaires up to 60 months;
7. To describe the occurence of adverse events of TOOKAD® Soluble -VTP treatment in patients with localized prostate cancer;
8. To describe the occurence of severe prostate cancer-related events: cancer extension to T3, metastasis and prostate cancer-related death;
9. To document the use of secondary prostate cancer therapies following TOOKAD® Soluble-VTP;
10. To describe the change in PSA from blood samples following TOOKAD® Soluble- VTP.

METHODOLOGY – STUDY DESIGN

This is a single center, single-arm, open-label, 60-month follow-up phase IIb clinical trial. Men with localized prostate cancer will receive TOOKAD® Soluble VTP under general anesthesia. Prior to the TOOKAD® Soluble VTP, patients will undergo routine ultrasound examination in the operating room for morphometric description of the prostate and to facilitate accurate treatment guidance for the treatment with TOOKAD® Soluble VTP. Treatment will then be applied to the prostate gland as a hemiablation procedure designed to destroy the lobe of the prostate gland that contains the Gleason score 7 (3+4) cancer. Afterwards, patients will be followed for 5 years (60 months) with clinical evaluation, questionnaires on QOL, erectile and urinary functions, and PSA testing. In addition, treatment outcomes will be assessed based on prostate biopsy results at 3, 12, 24, 36, 48 and 60 months after the TOOKAD® Soluble treatment. All patients will undergo biopsy at 3 and 12 months. Thereafter, biopsy will be performed for cause per institutional standards. If the Month 3 biopsy is positive for any cancer, patients will be allowed a single re-treatment by TOOKAD® Soluble VTP to one or both lobes. However, patients with evidence of clinical deterioration on the same side such as worsening Gleason score, increased core involvement with cancer tumor grades on the 3-month biopsy and/or rising PSA will be withdrawn from the study and proceed with standard care. In addition, patients who experience treatment related Grade 3-4 adverse events during their first treatment will not be re-treated at month 3 and will be proceed with standard care if the month-3 biopsy contains cancer, on the same or contralateral side.

This study is a phase IIb trial using optimal dose of TOOKAD® Soluble and optimal light-energy level conditions that were determined in previous phase I and II studies and confirmed by the phase III studies among patients with localized prostate cancer. Partial gland ablation therapy using thermal approaches, as an alternative to radical treatments for low-volume prostate cancer, is a treatment option currently being offered to men with prostate cancer in the U.S. as a tailored means to manage their disease with fewer side effects. Previous studies of TOOKAD® Soluble treatment have suggested that this non-thermal approach is an effective therapeutic strategy to achieve ablation of the prostatic tissue that contains the cancer lesion in this patient population. Considering the available clinical data, a phase IIb is considered appropriate at this stage, with the main aim of confirming, in intermediate risk patients, previous findings in low and favorable intermediate risk prostate cancer patients. Moreover, a single center design was also considered appropriate, as it allows for optimal standardization of the technique and better control over data acquisition.

NUMBER OF PATIENTS:

In order to obtain at least 44 evaluable patients, a total of 50 patients will be included and will be treated with TOOKAD® Soluble VTP in this study.

DRUG DESCRIPTION AND PREPARATION:

TOOKAD® Soluble - padeliporfin di-potassium (WST11) Drug Product is a dark coloured powder for solution for injection. It is packaged in amber glass vials. It is manufactured in two different presentations:

- 200 mg TOOKAD® Soluble in a 30 mL vial with blue flip-off cap, to be reconstituted, just before administration, with 20 mL of 5% dextrose solution for injection
- 400 mg TOOKAD® Soluble in a 50 mL vial with white flip-off cap, to be reconstituted, just before administration, with 40 mL of 5% dextrose solution for injection

The two presentations have the same formulation which is produced in exactly the same process and they differ only in the amount of TOOKAD® Soluble per vial,the size of the vial and the colour of the flip-off cap.

For both presentations the final concentration of TOOKAD® Soluble solution to be injected is 10 mg/mL.

INCLUSION CRITERIA:

Subjects will be eligible for inclusion in the study if all of the following criteria are met:

1. Men over 18 years of age.
2. Patients who have had a multiparametric MRI of the prostate performed and have undergone transrectal systematic biopsy plus biopsy of any volumes considered suspicious per the MRI (PIRADS version 2 score of 4 or 5) within 6 months before signing consent.
3. Histologic diagnosis of prostate cancer identifying Gleason score of 3+4 on one half of the prostate gland in no more than 2 sextants of the prostate gland and not present in more than 50% of any one core taken systematically. The involvement criterion does not apply to cores taken from MRI suspicious volumes.
4. Patients with concomitant Gleason score 3+3 prostate cancer in less than 50% of any core at any site will be considered eligible.
5. Prostate cancer stage up to cT2a – N0/Nx – M0/Mx.
6. Prostate volume ≥25 mL and ≤70 mL.
7. Serum PSA ≤10 ng/mL.

8. Men who are sexually active with women of childbearing potential must use contraceptive method with a failure rate of less than 1% per year. Contraception should be continued for a period of 90 days after the VTP procedure. The individual methods of contraception may be determined in consultation with the investigator.
9. Signed Informed Consent Form.

GENERAL EXCLUSION CRITERIA :

Subjects will not be eligible for the study if meeting any of the following criteria:

1. Unwillingness to accept the treatment;
2. Any prior or current treatment for prostate cancer, including surgery, radiation therapy (external or brachytherapy) or chemotherapy;
3. Any surgical intervention for benign prostatic hypertrophy;
4. Any condition or history of illness or surgery that might pose an additional risk to men undergoing the VTP procedure;
5. Life expectancy less than 10 years;
6. Participation in another clinical study involving an investigational product within 1 month before study entry;
7. Inability to understand the informed consent document, to give consent voluntarily or to complete the study tasks, especially inability to understand and fulfill the health-related QOL questionnaire;
8. Subjects in custody and or residing in a nursing home or rehabilitation facility;
9. Biopsy proven locally advanced or metastatic prostate cancer.

SURGERY AND OTHER TREATMENT-RELATED CONDITIONS OF EXCLUSION

Any condition or history of illness or surgery that may pose an additional risk to men undergoing the VTP procedure such as:

1. Any condition or history of illness or surgery that in the opinion of the investigator might affect the conduct and results of the study or pose additional risks to the subject (e.g., cardiac or respiratory disease precluding general anesthesia; anticoagulant treatment which cannot be temporarily withdrawn for the procedure).
2. Medical conditions that preclude the use of general anesthesia;
3. Any condition or history of active rectal inflammatory bowel disease or other factors which might increase the risk of fistula formation;

4. Hormonal manipulation (excluding 5-alpha-reductase inhibitors) that alters androgen production within the previous 6 months;
5. History of urethral stricture disease;
6. History of acute urinary retention within 6 months of study entry;
7. Anticoagulant drugs (e.g., warfarin) that could not be withdrawn during the 10 days prior to the VTP procedure or antiplatelet drugs (e.g. aspirin) that could not be withdrawn during the 10 days prior to the VTP procedure and 3 days after VTP;
8. Renal and hepatic disorders with values of >1.5 times the upper limit of normal (ULN) or blood disorders (upon clinician judgment);
9. A history of sun hypersensitivity or photosensitive dermatitis.

TREATMENT CONDITIONS

Subjects will fast per institutional standards before the VTP procedure in preparation for the use of anesthesia as per institutional standards. TOOKAD® Soluble VTP consists of the combination of a single, 10-minute IV infusion of TOOKAD® Soluble at the dose of 4 mg/kg, followed by the illumination of the zone to be treated with a 753-nm laser light delivered through transperineal interstitial optical fibers at a power of 150 mW/cm and light energy of 200 J/cm applied over 22 minutes and 15 seconds. Treatment for an individual patient is guided by the software TOOGUIDE TRUS, which is operated by the urologist and allows for the acquisition of TRUS images while the patient is in the treatment position, thus defining the prostate contours, the target and the optimal fiber configuration to maximize light dose in the target while sparing the surrounding tissues by allowing for a margin of at least 5 mm between the light delivery fibers and the rectal wall, the apex of the prostate, and the urethra. Fibers are then introduced into transparent catheters and positioned in the prostate areas of interest using a transperineal template. In case of unilateral disease, treatment of one lobe is applied. In case of bilateral disease, bilateral treatment is applied simultaneously or sequentially at the surgeon's discretion.

Re-treatment of lobes found positive for cancer at 3 months of follow-up is allowed. Re-treatment will be performed using the same drug and light dosing parameters as described for initial treatment and applied in the same manner. Re-treatment will be allowed 2-4 months following 3 month biopsy. Re-treatment may include either one (hemi gland) or both lobes (whole gland) of the prostate. As mentioned above, in case of signs of cancer progression on the same side or in case of treatment-related Grade 3-4 adverse events during their first treatment, patients will not be retreated and will be withdrawn and managed as per local standard of care, unless justification for continuing on study is specifically sought and approved from the IRB.

DURATION OF STUDY:

Patients will be followed until 60 months with assessment of the primary end-point at 12 month, and patients' questionnaires at 1, 3, 6 and 12 months and every 12 months until 60 months.

DURATION OF TREATMENT and STUDY PROCEDURES:

The VTP procedure can be planned, following surgeon's advice, as a day-case surgery. Patients will be hospitalized in the morning of the day of the procedure. The procedure is done in the operating room under general anesthesia. The total duration of the procedure is about 1 ½ to 2 hours (including anesthesia, fiber placement and illumination with the laser light). This includes a 10 minutes infusion of TOOKAD® Soluble, followed immediately by light delivery over approximately 22 minutes.

After treatment the subject will recover under routine postoperative monitoring in a dimmed room for at least 6 hours and will be discharged on the day of the procedure following this interval, unless the investigator feels that the patient should be hospitalized longer for medical reasons. Urinary catheter will be kept at least 6h after the VTP procedure.

CRITERIA FOR EVALUATION:

Primary endpoints

- Binary response to treatment defined as absence of Gleason grade 4 or 5 on biopsy at month 12.

Secondary endpoints

- Binary response to treatment defined as the absence of any Gleason grade 4 or 5 biopsy on or before months 24, 36, 48 and 60. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of gleason grade 4 or 5, the subject will be considered to have responded;
- Binary response to treatment defined as the absence of any prostate cancer on biopsy on or before months 3, 12, 24, 36 and 60. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of any cancer, the subject will be considered to have responded;
- Binary response to treatment defined as the absence of any Gleason grade 4 or 5 biopsy on or before months 12, 24, 36, 48 and 60 in the treated lobe. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of gleason grade 4 or 5, the subject will be considered to have responded;
- Binary response to treatment defined as the absence of any prostate cancer on biopsy on or before months 3, 12, 24, 36, 48 and 60 in the treated lobe. If a subject is retreated following

a positive biopsy at 3 months and subsequent biopsy shows absence of any cancer, the subject will be considered to have responded;

- Changes in biopsy result between 3, 12, 24, 36, 48 and 60 months after the procedure.
- Patients' reported outcome measures (PROMs) impairment: urinary symptoms using IPSS and erectile functions using IIEF prior to treatment beginning and then 1, 3, 6, 12, 24, 36, 48 and 60 months after completing treatment
- Severe prostate cancer-related events: cancer extension to T3, metastasis or prostate cancer-related death
- Use of secondary prostate cancer treatment following VTP will include surgical removal of the prostate gland, radiation treatment to the prostate gland, use of hormone or chemotherapies.
- Adverse events
- Serum PSA measurements in ng/mL.

SAMPLE SIZE JUSTIFICATION

A proportion of responders of r=70% at 12 months is considered to be a clinically significant expectation in localized intermediate-risk prostate cancer patients.

Based on historical data in similar series of patients, a minimum of N=44 patients is required to test the null hypothesis H0: "r≤70%" vs. H1: "r>70%", with 80% power and 5% as alpha risk.

MANUFACTURING INVESTIGATIONAL PRODUCT:

TOOKAD® Soluble is manufactured by Praxis Pharmaceutical S.A, Vitoria-Gasteiz, Spain.

TOOKAD® Soluble batches are released by Steba Laboratories, Ness Zion, Israel.

Laser equipment: Intermedic Arfran S.A, Spain

FLOW CHART: Schedule of Events

Procedure	V1 and screening period	V2 VTP	V3 Day 7+/- 2 days	V4 Month 1 +/- 1 wk	V5 Month 3 +/- 2 wks	V6 Month 6 +/- 2 mos	V7 Month 12 +/- 2 mos	V8-11 Annual f/u +/- 3 mos
Informed Consent	x							
Inclusion/exclusion Criteria	x							
Medical History	x							
TNM Staging	x							
VTP Treatment		x						
Clinical Examination	x	x[a]						
Prostate Biopsy	x[b] ≤6mos before consent				x[c]		x	x[d]
Digital Rectal Examination	x							
Prostate Specific Antigen	x[e]	x		x	x	x	x	x
Standard Hematologic Tests	x[e]	x[a]		x	x	x	x	x
Standard Blood Chemistry Tests	x[e]	x[a]		x	x	x	x	x
Standard Blood Coagulation Tests	x[e]							
Additional Inclusion Blood Tests	x[e]							
Prostate Volume	x	x						
MRI	x[d]				x		x	x[d]
Patient-Reported Outcome Measures (PROMs)	x			x	x	x	x	x
Study Medication		x						
Concomitant Medications	x	x[a]	x	x	x	x	x	x
Adverse Events		x[a]	x	x	x	x	x	x

[a] Before and after VTP procedure

[b] In case of unilateral disease, focal treatment of one lobe will be applied. In case of bilateral disease (discovered at entry or during follow-up), bilateral treatment will be applied consecutively or simultaneously.

[c] Visit at 3 months (± 2 weeks). Retreatment of lobes found positive for cancer will be allowed 2-4 months following positive biopsy, except in case of cancer progression on the same side or grade 3-4 related AE during the first treatment unless justification for continuing on study is specifically sought and approved from the IRB.

[d] As performed per standard of care

[e] Obtained at V1 or available in the patient file if < 4 weeks before V1

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
5-ARI	5-Alpha Reductase Inhibitor
AE	Adverse Event
ALT	Alanine Aminotransferase
AMD	Age-related Macular Degeneration
APTT	Activated Partial Thromboplastin Time
AS	Active Surveillance
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
COMP	Comprehensive Metabolic Panel
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
DLI	Drug-Light Interval (the interval between start of infusion and start of illumination)
DRE	Digital Rectal Examination
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EPIC	Expanded Prostate Cancer Index Composite
F(VOA)	Focal Vascular Occluding Agent
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous

LDI	Light Density Index
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
PDT	Photodynamic Therapy
PICF	Patient Informed Consent Form
PROMs	Patient Reported Outcome Measures
PSA	Prostate Specific Antigen
PTT	Partial Thromboplastin Time
QoL	Quality of Life
ROS	Reactive Oxygen Species
RP	Radical Prostatectomy
SAE	Serious Adverse Event
SAS	Stastitical Analysis System
SOC	System Organ Class
SOP	Standard Operating Procedure
TG	Treatment Guidance
TRUS	TransRectal Ultrasound
TURP	TransUrethral Resection of the Prostate
US	UltraSound
VEGF	Vascular Endothelial Growth Factor
VTP	Vascular-Targeted Photodynamic therapy
WHO	World Health Organisation

2 BACKGROUND INFORMATION

2.1 Prostate Cancer: risk stratification and Treatment

Prostate cancer is one of the most common cancers in American men and a leading cause of cancer related suffering and mortality.[1] The incidence in 2012 was estimated at 413,000 new cases in the Americas and over 85,000 deaths. In the European Union, prostate cancer is the most commonly diagnosed cancer in men, and the third cause of cancer-related death.[2] In 2009, prostate cancer was the second most common cause of cancer-related death in US males and the leading type of cancer in men, with one-third of new cancer cases. [3]

Tumor stage and Gleason grade, used as the main predictors of risk in prostate cancer, have demonstrated a trend over time toward lower risk disease in US men. Among patients diagnosed with this disease, 46% are reported as being at low risk, 30% at intermediate risk, and 24% at high risk according to the D'Amico classification.[4,5] The widespread adoption of PSA screening in clinical practice has led to an increased proportion of disease being diagnosed earlier when tumors are smaller and at lower stage[4,6], resulting in a very high rate of treatment among younger men and additional societal burden[7,8]. Despite technological refinements in surgery and radiation therapy, radical whole-gland therapies cause erectile dysfunction in 30-70%, incontinence (requiring pad usage) in 5-10%, and rectal symptoms (diarrhea, bleeding, proctitis) in 5-20% of treated patients.[9] New forms of conservative management designed to avoid treatment related toxicities have been developed to adapt to this shift toward smaller volume cancers identified at an earlier stage and are now being used in the U.S. and elsewhere, as an alternative to whole gland therapies.[10,11,12,13,14,15]

These therapies which involve partial gland soft tissue ablation, also called focal therapy, are designed to appropriately address low volume prostate cancer at the proper scale to control the disease while maintaining normal organ function and have become standard therapies at U.S. centers.

Vascular-Targeted Photodynamic (VTP) therapy uses light delivered through optical fibers inserted in the tissue to activate circulating TOOKAD® Soluble (WST11;padeliporfin di-potassium) after its intravenous (IV) administration, in order to produce instantaneous vessel occlusion and subsequent tissue necrosis.[16,17,18,19] By confining fiber placement to the prostatic tissue that contains the target tumors TOOKAD® Soluble-VTP offers the means to treat patients with early prostate cancer through partial gland ablation in a minimally invasive manner. TOOKAD® Soluble-VTP has a particular appeal in oncology because it does not preclude the use of other treatment modalities. Finally, TOOKAD® Soluble-VTP of the prostate is applicable in an ambulatory care setting and may be used as a repeatable procedure.

Localized treatment using TOOKAD® Soluble may offer an effective alternative to radical therapy in appropriately selected patients. This non-thermal form of partial gland ablation (PGA) is confined to the cancer containing prostate tissue while preserving adjacent normal tissue and, as a consequence, maintain organ functions. In localized. low-risk prostate cancer, hemiablation of the gland with TOOKAD®

Soluble VTP has been shown, in prospective clinical trials, to be an effective form of treatment with minimal side effects and negligible collateral damage to surrounding tissues. These results are in contrast to other forms of prostate hemiablation (e.g. cryotherapy and high intensity focused ultrasound (Hi-Fu)), which are thermal and have shown detrimental injury to surrounding tissues and greater impact on quality of life outcomes.[20,21,22] TOOKAD® Soluble VTP is a novel type of treatment particularly addressed to patients who have early-stage disease (namely low and intermediate-risk patients). Patients successfully managed with this approach may then be spared the noxious secondary effect of radical treaments. This treatment, therefore, is designed to optimize quality of life outcomes while providing a means of controlling cancer progression in early stage patients that offers a management approach commensurate to the extent of their cancer.

2.2 TOOKAD® Soluble VASCULAR-TARGETED PHOTODYNAMIC THERAPY (VTP)

2.2.1 Historical Development

With a discovery program beginning in 2000, STEBA BIOTECH has developed a novel approach that relies on the bacteriochlorophyll derivatives, a novel generation of photosensitizers with unique attributes.The first compound of this family developed in prostate cancer was WST09. Several studies in patients with recurrent or previously untreated prostate cancer showed very promising results. WST11 (TOOKAD® Soluble) is a hydrophilic compound that is soluble in aqueous solutions and may be considered as the first in a class of focal vascular occluding agents.

2.2.2 Chemical, Photophysical, and Photochemical Properties

Chemically, WST11 is palladium bacteriopheophorbide monolysotaurine and is also known as padeliporfin-di-potassium. Its empirical formula is C37H41K2N5O9PdS, and its molecular mass is 916.4 $g.mole^{-1}$. The ultraviolet/visible spectrum of the drug product in plasma presents 5 maxima (at 276 nm, 334 nm, 384 nm, 518 nm, and 753 nm).

2.2.3 Non-clinical Studies

Updated information on the non-clinical studies of WST11 may be found in the Investigator's Brochure and in the study protocol.

2.2.3.1 Safety pharmacology

Effects on the central nervous system, respiratory system, and the bleeding time were assessed in male rats following IV administration. WST11 caused no serious effects on any of these functions, except for minor effects (bronchodilation) at the highest dose used in the prostate treatment setting (150 mg/kg IV). Experiments using human embryonic kidney cells suggested that WST11 would possess a very low liability for prolonging the QT interval. WST11 administered by the IV route at single doses did not induce statistically significant changes in arterial blood pressure, heart rate or the electrocardiogram (ECG) in conscious cynomolgus monkeys. These results suggested that the No Observed Effect Level (NOEL) of WST11 formulated in dextrose 5% at 5 mg/mL corresponds to 50 mg/kg in conscious animals. WST11

administered at the dose of 50 mg/kg, 25 mg/kg and 20 mg/kg induced a tendency to bradycardia associated with vomiting at all dose levels, with hypotension only at 50 mg/kg. Despite vomiting observed in one animal only, and despite the tendency to bradycardia, the dose of 25 mg/kg (16 mL/min) was considered to be the No Observed Adverse Effect Level (NOAEL) of WST11. No local intolerability was attributed to WST11 after dosing by the IV, intra-arterial or perivenous routes in rabbits.

2.2.3.2 Pharmacokinetics

The distribution of WST11 in tissues was evaluated in male rats after a single IV injection at the dose of 10 mg/kg by the distribution of its palladium atom. Measurable concentrations of palladium were observed only in the first sampling times in plasma, blood cells, liver, lung, and kidney. This suggests a low probability of phototoxicity when using the molecule, as the eyes and skin had very low concentration. In vitro, the WST11 plasma protein binding percentage was 98.97%.

2.2.3.3 Toxicology

When administered to the mouse and to the rat in single IV doses, WST11 induced mortality from 200 mg/kg in mice and from 300 mg/kg in rats. In both species, WST11 induced several clinical signs at 200, 300 and 400 mg/kg. Consequently, the NOEL in the mouse and in the rat after single administration was 100 mg/kg under the defined conditions. In a 4-week toxicity study followed by a 2-week treatment-free period to evaluate the regression of toxic signs, WST11 was well tolerated in the rat, except for the induction of transient subdued behavior at 75 and 150 mg/kg/day. No target-organ was identified. The NOAEL was identified as 150 mg/kg/day. WST11 administered for 7 days to cynomolgus monkeys produced vomiting and signs of intolerance at 100 and 150 mg/kg/day; therefore, the NOAEL was identified as 50 mg/kg/day. In a 2-week IV toxicity study in the cynomolgus monkeys followed by a 2-week treatment-free period, WST11 produced vomiting, prostration, reduced activity and decreased food consumption at 150 mg/kg/day. Dose levels considered very high compared with the intended dose in human induced a decrease in heart rate, particularly marked at 30 minutes after dosing. However, the values tended to return to normal at 3 hours after dosing. Consequently, the NOAEL was assessed as 25 mg/kg/day.

2.2.3.4 Studies relevant to the intended therapeutic use

One study evaluated the dose-escalating effect of a 10-minute IV infusion of WST11 followed by light activation with a 753 nm diode laser on the normal prostate of old mongrel dogs, with illumination using different light fluence rates initiated 5 minutes following the start of infusion. Animals were monitored during the procedure as well as daily, with necropsies after 8 days. No major secondary effects, changes in heart rate, oxymetry or body temperature were observed. Macroscopic analysis showed evidence of hemorrhagic damage. Morphometric analyses of the prostate revealed that VTP therapy induces necrosis. Findings from the combination of increasing doses of WST11 and energies revealed that a threshold level was needed to show evidence of necrosis. Energy was also shown to be critical. There was no evidence of thrombosis in the other organs, confirming that the phenomenon is local.

One study was conducted to evaluate the safety and efficacy of WST09 and WST11 in the prostatic tissue of 12 dogs, as well as the pharmacokinetics and other safety parameters over 24 hours post-injection. The results suggested that with 200 J/cm, WST11 at 2 mg/kg induced slightly less severe parenchymal and capsular damage than, while WST11 at 5 mg/kg at 200 J/cm and 400 J/cm induced an amount of parenchymal necrosis comparable to, WST09 at 2 mg/kg.

2.2.4 Clinical Studies

A phase I study conducted in young healthy male subjects showed that intravenous injections of TOOKAD® Soluble are well tolerated up to the dose of 15 mg/kg.

TOOKAD® Soluble treatment of localized prostate cancer comprises several steps: (i) identification of the target using biopsy; (ii) preparation of a treatment guidance by the urologist using the software TOOGUIDE® TRUS where transrectal ultrasound (TRUS) images of the prostate are used to define the number, position and illumination length of fibers required to treat the target. Fiber's illumination is provided by end diffusers of a preferred length from 1 to 5 cm. This allows light delivery adjustment to the target tissue volume and geometry at a given prostate location.; (iii) transperineal insertion of the conducting optical fibers in the lobe of the prostate to be treated (under general anesthesia); (iv) IV infusion of the photosensitiser TOOKAD® Soluble at a standard dose of 4 mg/kg; (v) activation of the circulating TOOKAD® Soluble by laser light delivered through the conducting optical fibers. The energy delivered per fiber is standardised to 200 J/cm.

The phase II studies conducted in low-risk prostate cancer patients in Europe, Canada and the US have shown a correlation between the total energy delivered and efficacy results, thus allowing the determination of optimal treatment conditions with TOOKAD® Soluble (4 mg/kg, 200 J/cm and light density index [LDI] ≥1, see section 6.2.4 below)[23]. Moreover, such studies have shown that TOOKAD® Soluble treatment of localized prostate cancer renders a significant percentage (at least 80%) of patients free from prostate cancer in the treated lobe(s) at follow-up biopsies, with minimally impaired erectile and urinary functions as compared with baseline, and with a good safety profile.[24] In the largest study, 83% of the patients treated with optimal treatment conditions who underwent prostate biopsy at 6 months had negative histopathology for prostate cancer in the treated lobe.[25]

The pivotal European randomized phase III study demonstrated the benefit of TOOKAD® Soluble VTP compared to active surveillance. The analysis met both co-primary efficacy endpoints; TOOKAD® Soluble VTP significantly doubled time to progression from low-risk to moderate or high-risk prostate cancer (from 14.1 to 28.3 months; $p < 0.001$), significantly reduced the defined failure rate within 24 months after treatment (HR = 0.34; $p < 0.001$), and increased the probability of a negative biopsy at 24 months by 3.62 times (from 13.5 to 49.0%; $p < 0.001$). The robust quality of these outcomes was evidenced by the consistency of results across all 3 analysis populations (ITT, mITT, PP) and the 2 disease status subgroups (unilateral disease or bilateral disease).

Secondary efficacy endpoints also demonstrated the advantages of TOOKAD® Soluble VTP to active surveillance. The strongly positive and statistically significant ($p < 0.001$) effect of TOOKAD® Soluble VTP on the objective of focal therapy, i.e., reduction of tumour burden, indicates that the effect on disease progression may continue beyond the 24 months observed in this study. Substantial reduction in need for radical therapy, occurrence of T3 prostate cancer, and metastatic disease provide meaningful clinical outcomes for men with low-risk, localised prostate cancer.

TOOKAD® Soluble VTP resulted in a safety profile similar to the comparator in this study, active surveillance, and potentially superior to radical therapy, the alternative for management of low-risk prostate cancer. The AE profile of TOOKAD® Soluble VTP was similar to that of active surveillance except for events specifically related to the drug itself, the delivery device, or the procedure. Most of these related AEs were expected and occurred during the procedure or in the days after the procedure and resolved without sequelae. The numbers of subjects experiencing an AE related to the drug, device, or procedure (78.7%) or an SAE related to the drug, device, or procedure (15.2%) are reasonable considering the invasive aspects of this minimally invasive procedure. Urinary function and erectile function were well maintained with only transient increase in associated symptoms after the procedure. The safety profile for TOOKAD® Soluble VTP compares very favourably with radical therapies, particularly with regard to the preservation of erectile function.

The good safety profile observed in this study is probably related to the confined nature of the biological cascade of events triggered by the near infra red activation of TOOKAD® Soluble in the target tissue vasculature. In contrast to other focal techniques which utilize non-selective thermal radiation, this cascade of events rapidly results in the occlusion and destruction of small vessels followed by non-thermal coagulative necrosis of the target tissue with minimal thermal dispersion to surrounding tissues. This unique therapeutic effect was confirmed by the follow-up MRI obtained 7 days after the TOOKAD® Soluble VTP procedure that demonstrated confluent necrosis that closely contours the prostate capsule within the treated lobe. It is important to note that although extra-prostatic necrosis was seen in most treated subjects, it was usually minimal (mean volume = 2.98 mL) and of minimal clinical significance.

The completed Latin American trial (PCM304) was conducted to test the efficacy of TOOKAD® Soluble VTP treatment (applied as hemiablation) in men with larger volume cancers, including those with bilateral Gleason 3+3 and 3+4 cancer. The study showed similar results to those obtained in prior Phase II studies and thereby confirmed the treatment applicability to patients with more advanced cancers. Selection criteria and treatment parameters were compatible with those of the current trial (PCM204). In the intent to treat (ITT) population of 81 men, 12 men had Gleason 3+4 cancer and 69 had Gleason 3+3. In the ITT group, 60 (74%) had negative biopsies at 12 months, although 8 patients did not undergo end of protocol biopsy. Of the 73 evaluable per protocol patients who completed end of study 12-month biopsies, 58 (80%) had negative biopsies. Out of the 12 patients who had Gleason 3+4 cancer at entry, two where withdrawn prior to receiving the study drug because of a history of TURP (exclusion criteria) discovered during the pretreatment ultrasound examination of the prostate and two others did not have the Month

6 and Month 12 prostate biopsies because of adverse events (stroke and perineal pain respectively). As a result, only 8 patients had evaluable Month 6 and Month 12 prostate biopsies. Of those 8 evaluable patients with Gleason 3+4 prostate cancer treated, 8 (100%) had negative end of study biopsies (Detailed in Table # 1 in appendix 13). None underwent subsequent treatment over the study interval.

Safety data was also similar to prior published studies, demonstrating grade 3 events in 9% of patients consisting mainly of manageable infectious, urinary or GI related complications. No grade 4 or 5 events occurred. Erectile and urinary functional outcomes were likewise minimally affected. Collectively these studies have helped to demonstrate treatment efficacy in men with low and intermediate risk disease using these selection parameters.

2.2.5 Standardization and evaluation of TOOGUIDE TRUS Treatment Guidance for VTP with TOOKAD® Soluble

The Treatment Guidance includes:

- An assessment of the volume of the prostate using TRUS images.
- The computer determination of the number, length and position of fibers ensuring security margins of 5 mm between the illuminated fibers and the boundary of the gland.
- TOOGUIDE TRUS software used for the treatment guidance is described in

Appendix 6.

3 TRIAL OBJECTIVES AND PURPOSE

3.1 Study rationale

Based on the positive phase II and phase III studies conducted in the United States, Europe, Canada and Latin America, it is expected that TOOKAD® Soluble VTP treatment for localized prostate cancer will result in a significant percentage of patients becoming cancer-free, with minimal change from baseline erectile and urinary function and with a good safety profile. These findings have thus far been consistent across the trials in low volume Gleason 3+3 prostate cancer, a disease considered to be low-risk. Among trial participants in the completed Latin American study (PCM304), where few patients with intermediate-risk Gleason score 3+4 cancer were treated, treatment results appear similar to those treated men with Gleason 3+3 disease. Therefore, establishing the safety and efficacy of this procedure specifically in men with localized, intermediate risk prostate cancer is an important research objective to be addressed in this study. Interest in performing this study in the U.S. at a center of excellence will provide rigorous evaluation of the technique and oncologic outcomes as well as detailed study of functional metrics.

3.2 Primary objective

- To evaluate for the absence of biopsy detectable Gleason grade 4 or 5 prostate cancer on 12-month, post-treatment biopsy following TOOKAD® Soluble- VTP in men with Gleason score 7 (3+4) prostate cancer.

3.3 Secondary objectives

1. To describe the rate of responders, with response defined as the absence of any Gleason grade 4 or 5 biopsy on or before months 24, 36, 48 and 60. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of gleason grade 4 or 5, the subject will be considered to have responded;
2. To describe the rate of responders, with response defined as the absence of any prostate cancer on biopsy on or before months 3, 12, 24, 36, 48 and 60. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of any cancer, the subject will be considered to have responded;;
3. To describe the rate of responders, with response defined as the absence of any Gleason grade 4 or 5 biopsy on or before months 12, 24, 36, 48 and 60 in the treated lobe. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of gleason grade 4 or 5, the subject will be considered to have responded;
4. To describe the rate of responders, with response defined as the absence of any prostate cancer on biopsy on or before months 3, 12, 24, 36, 48 and 60 in the treated lobe. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of any cancer, the subject will be considered to have responded;
5. To describe the change in biopsy results between 3, 12, 24, 36, 48 and 60 months after TOOKAD® Soluble-VTP.
6. To describe changes in urinary and erectile function and their potential impact on QOL using International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF) questionnaires up to 60 months;
7. To describe the occurence of adverse events of TOOKAD® Soluble VTP treatment in patients with localized prostate cancer;
8. To describe the occurence of severe prostate cancer-related events: cancer extension to T3, metastasis and prostate cancer-related death.

9. To document the occurence of secondary prostate cancer therapies following VTP treatment.
10. To describe changes in PSA from blood samples following TOOKAD® Soluble-VTP.

4 TRIAL DESIGN

4.1 Overall study design and plan

This is a single center, single-arm, open-label, 60-month follow-up phase IIb clinical trial. Men with localized prostate cancer will receive TOOKAD® Soluble -VTP treatment under general anesthesia. Prior to the TOOKAD® Soluble- VTP treatment, patients will undergo routine ultrasound examination in the operating room for morphometric description of the prostate and to facilitate accurate treatment guidance for the treatment with TOOKAD® Soluble- VTP. Treatment will then be applied to the prostate gland as a focal therapy, hemiablation procedure designed to detroy the lobe of the prostate gland that contains the Gleason score 7 (3+4) cancer. Afterwards, patients will be followed for 12 months with clinical evaluation, questionnaires on QOL, erectile and urinary functions, and PSA testing. In addition, treatment outcomes will be assessed based on prostate biopsy results at 3, 12, 24, 36, 48 and 60 months after the TOOKAD® Soluble treatment. All patients will undergo biopsy at 3 and 12 months after the TOOKAD® treatment. Thereafter, biopsy will be performed for cause per institutional standards. If the Month 3 biopsy is positive for any cancer patients will be allowed a single re-treatment by TOOKAD® Soluble VTP. However, patients with evidence of clinical deterioration on the same side such as worsening Gleason score, increased core involvement with cancer tumor grades on the 3-month biopsy and/or rising PSA will be withdrawn from the study and proceed with standard care. In addition, patients who experience treatment-related Grade 3-4 adverse events during their first treatment will not be re-treated at month 3, will be withdrawn and proceed with standard care if the month-3 biopsy contains cancer on the same or contralateral side, unless justification for continuing on study is specifically sought and approved from the IRB.

4.2 Discussion of study design

This study is a phase IIb trial using optimal dose of TOOKAD® Soluble and optimal light-energy level conditions that were determined in previous phase I and II studies among patients with localized prostate cancer and confirmed in recent phase III studies. Partial gland ablation therapy, as an alternative to radical treatments for low-volume prostate cancer, is a treatment option currently being offered to men with prostate cancer in the U.S. as a tailored means to manage their disease with fewer side effects. As previous studies of TOOKAD® Soluble treatment have suggested, this is an effective therapeutic strategy in this patient population. Considering the available clinical data, a phase IIb study is considered appropriate at this stage, with the main aim of confirming in intermediate risk patients previous findings in low and low-

intermediate risk prostate cancer patients. Moreover, a single center design was also considered appropriate, as it allows for optimal standardization of the technique and better control over data acquisition.

5 SELECTION AND WITHDRAWAL OF SUBJECT

5.1 Subject Screening

Patients will be identified by the study investigators based on a previously performed transrectal ultrasound guided biopsy. As a patient is identified by the Investigator as a potential study participant, informed consent will be sought and obtained. Following provision of their informed consent, the patient will receive a copy of the consent document and the Investigator will schedule Visit 1. Each patient will, at this time, be considered enrolled and will be allocated a study number.

Should a patient provide consent, attend Visit 1 and subsequently be considered ineligible, due to an inclusion criterion not being met (e.g., PSA levels from the baseline Visit 1 sample return as >10 ng/ml), or an exclusion criterion being met (e.g., ECG reading at Visit 1 proves the patient to be ineligible), these patients will be considered screen failures and their patient number will not be reallocated.

5.2 Inclusion Criteria

Subjects will be eligible for inclusion in the study if all of the following criteria are met:

1. Men over 18 years of age;
2. Patients who have had a multiparametric MRI of the prostate performed and have undergone transrectal systematic biopsy plus biopsy of any volumes considered suspicious per the MRI (PIRADS version 2 score of 4 or 5) within 6 months before signing consent;
3. Histological diagnosis of prostate cancer identifying Gleason score of 3+4 on one half of the prostate gland (right or left) in no more than 2 sextants of the prostate gland and not present in more than 50% of any one core taken systematically. The involvement criterion does not apply to cores taken from MRI suspicious volumes;
4. Patients with concomitant Gleason score 3+3 prostate cancer in less than 50% of any core at any site will be considered eligible;
5. Prostate cancer stage up to cT2a – N0/Nx – M0/Mx;
6. Prostate volume ≥25 mL and ≤70 mL;
7. Serum PSA ≤10 ng/mL;

8. Men who are sexually active with women of childbearing potential must use contraceptive method with a failure rate of less than 1% per year. Contraception should be continued for a period of 90 days after the VTP procedure. The individual methods of contraception may be determined in consultation with the investigator;
9. Signed Informed Consent Form.

5.3 General Exclusion Criteria

Subjects will not be eligible for the study if meeting any of the following criteria:

1. Unwillingness to accept the treatment;
2. Any prior or current treatment for prostate cancer, including surgery, radiation therapy (external or brachytherapy) or chemotherapy;
3. Any surgical intervention for benign prostatic hypertrophy;
4. Any condition or history of illness or surgery that might pose an additional risk to men undergoing the VTP procedure;
5. Life expectancy less than 10 years;
6. Participation in another clinical study involving an investigational product within 1 month before study entry;
7. Inability to understand the informed consent document, to give consent voluntarily or to complete the study tasks, especially inability to understand and fulfill the health-related QOL questionnaire;
8. Subjects in custody and or residing in a nursing home or rehabilitation facility;
9. Patients with pre-treatment MRI evidence of seminal vesical or lymph node involvement (cross sectional nodes > 15 mm) will require biopsy negative confirmation to be considered eligible and approval at the discretion of the Principal Investigator.

5.4 Surgery and other Treatment-Related Conditions of Exclusion

Any condition or history of illness or surgery that may pose an additional risk to men undergoing the TOOKAD® Soluble -VTP procedure such as:

1. Any condition or history of illness or surgery that in the opinion of the investigator might affect the conduct and results of the study or pose additional risks to the subject (e.g., cardiac or respiratory disease precluding general anesthesia; anticoagulant treatment which cannot be temporarily withdrawn for the procedure).
2. Medical conditions that preclude the use of general anesthesia;

3. Any condition or history of active rectal inflammatory bowel disease or other factors which might increase the risk of fistula formation;
4. Hormonal manipulation (excluding 5-alpha-reductase inhibitors) that alters androgen production,within the previous 6 months;
5. History of urethral stricture disease;
6. History of acute urinary retention within 6 months of study entry;
7. Anticoagulant drugs (e.g., warfarin) that could not be withdrawn during the 10 days prior to the VTP procedure or antiplatelet drugs (e.g. aspirin) that could not be withdrawn during the 10 days prior to the VTP procedure and 3 days after VTP;
8. Renal and hepatic disorders with values of >1.5 times the upper limit of normal (ULN) or blood disorders (upon clinician judgment);
9. A history of sun hypersensitivity or photosensitive dermatitis.

5.5 End of study

5.5.1 Study Completion Procedures

Subjects will be considered to have completed the study when they have completed all examinations up to and including the Month 60 visit.

5.5.2 Log of Exit from the Study

A subject exit form must be completed for each subject who exits the study for any reason, indicating whether the subject is withdrawing (providing the reason if available), is terminated from the study, or is considered lost-to-follow-up. Before a subject is considered “lost-to-follow-up”, there must be three documented attempts to reach him. At least one of these attempts must be in writing by certified/return receipt mail, a copy of which must be included in the subject’s medical/clinic chart.

5.5.3 Exit from the Study

Subjects will have the right to withdraw from participation in the study at any time, for any reason.

Subjects may be withdrawn from the study at the discretion of the Investigator only if continuation will jeopardise the subjects’ health and/or welfare. Every effort must be made to follow withdrawn subjects for safety reasons using the appropriate CRFs until the planned end of the study period.

5.5.4 Subject withdrawal

The criteria for terminating participation in the study are detailed below:

1. Serious adverse event that is study-related (see definition further below), as recommended by the Investigator, patients with grade 3 or 4 adverse events following their initial treatment who have evidence of treatable prostate cancer on month 3 biopsy will not undergo re-treatment, will be withdrawn from the study and proceed with standard of care unless justification for continuing on study is specifically sought and approved from the IRB.
2. Subject withdrawal: at any time, a subject can withdraw from the study at his request or on the basis of the Investigator's clinical judgment.
3. Patients with evidence of clinical deterioration on the same side such as Gleason grade 5 cancer, more than 2 sextants including Gleason grade 4 cancer on the treated side on the 3-month re-biopsy will be withdrawn from the study and proceed with standard care.
4. Major protocol violation, defined as any violation that may impact the safety of a study subject,.
5. Termination of the study by the Sponsor.

5.5.5 Stopping Rules

The study medication administration and the light delivery are planned to last no longer than approximately 32 minutes. This time will be precisely monitored. The drug or light administration can be discontinued at any time by the investigator in case of a significant adverse event (AE).

Because this study consists of a single administration of the study medication and a single session of light delivery, there is no need to establish rules for stopping the study treatment during the follow-up period.

The Sponsor may terminate the study at any time in a center:

1. If the investigator is non-compliant with the protocol, the regulatory requirements or the ICH-GCP;
2. If the CRF completion or drug accountability is inadequate, and the investigator is unable to take corrective action in any of these cases;
3. In case of failure to recruit subjects.

The entire study may be terminated for medical reasons. In addition the Sponsor retains the right to end the study at any time if the study cannot be carried out as agreed upon in the study protocol. In case of premature termination the Investigators, IRB/IECs and regulatory authorities will be informed by the Sponsor.

The Sponsor also reserves the right to terminate the study at any time for administrative reasons. The Sponsor will not reimburse the Investigator for the evaluation of subjects if the evaluations are conducted in a manner other than that specified in this protocol.

5.5.6 Replacement of premature withdrawals from trial

The Sponsor reserves the right to replace a subject who is removed or withdraws from the study before the month 3 biopsy with a new subject. A subject who is removed or withdraws after the month 3 biopsy will not be replaced.

6 TREATMENT OF SUBJECTS

6.1 Entry into study

6.1.1 Entry Biopsy

Only patients with at least one prior prostate biopsy will be considered. Additionally:

- The biopsy must demonstrate any Gleason score 7 (3+4) prostate adenocarcinoma in 1 or 2 sextants on one side of the prostate gland.
- The biopsy must include a minimum of 12 cores and must have at least 1 core from each prostate sextant.
- All cores from the prior biopsy must have been evaluated and results confirmed at the treating institution.
- Standard definition for prostate sextant anatomy will be used: Right and Left; Apex, Mid and Base. Transition zone biopsies, if present, will be considered as Mid gland.
- Targeted biopsy of suspicious lesions seen on MRI that meet PIRADS (version 2) criteria for level 4 or 5 lesions will be required before patients may be considered eligible.
- Patients who meet initial biopsy eligibility criteria with PIRADS (version 2) criteria lesions of level 3 or less will not require targeted biopsy.
- If a patient has undergone biopsy without MRI and subsequently undergoes MRI but no suspicious (PIRADS 4 or 5) lesions are observed, additional biopsy is not needed for inclusion.

6.1.2 Consent to participate

Patients will be enrolled if they have given written consent to participate. They will be informed of the local and international recommendations for the treatment of their condition (localized prostate cancer) and the nature of the available interventions.

6.1.3 Assignment of Subject Identification

A subject identification number will be assigned in the CRF at Screening. This identification number should be used in every study-related documents. To maintain confidentiality, the subject's name should not be

recorded on any study document other than the informed consent form. This identification number differs from the treatment number(s) that will be assigned and reported in the CRF on the day of the VTP procedure.

6.2 Treatment Guidance (TG)

6.2.1 Aim of Treatment Guidance

The aim of the treatment guidance is to determine the optimal light dose by estimating the number of fibers and for each fiber its position regarding the external template and the length of its diffusing tip.

This fibers configuration defines the treatment effect boundaries (in 3 dimensions).

6.2.2 TOOGUIDE TRUS Treatment Guidance software

The Treatment Guidance is done with the aid of the Treatment Guidance Software TOOGUIDE TRUS (see Appendix 6). The procedure is performed or supervised by the urologist in charge with the treatment.

TOOGUIDE TRUS allows acquiring TRUS images of the patient while he is in the treatment position, to define the prostate contours, the target and the optimal fibers configuration to maximize light dose in the target while sparing the surrounded tissues.

6.2.3 Treatment Conditions

Treatment guidance will help to determine the number and position of laser fibers to be inserted, with the length of illumination necessary to achieve a Light Density Index ≥ 1 in the targeted tissue. In case of unilateral disease, focal treatment of one lobe will be applied. In case of bilateral disease (discovered at entry or during follow-up), bilateral treatment will be applied consecutively or simultaneously. Retreatment of lobes found positive for cancer at 3-months follow-up will be allowed, provided there is no sign of cancer progression in the treated lobe and the patient did not experience grade 3 or 4 adverse events.

6.2.4 Definition of the Light Density Index (LDI)

The Light Density Index (LDI) is defined, for each zone to be treated, as the ratio of the cumulative length of illumination tip of the fibers (in cm) per cubic centimeter of the targeted zone. It is calculated as:

LDI = Total length of illumination tips of the fibers (in cm) / Treatment volume (in cc)

Where:

1. The total length of illumination tip of the fibers is the sum (in centimeters) of the length of each illumination tip of the fibers used during the procedure for the treated lobe.
2. The treatment volume (in cc) is calculated by the TOOGUIDE- TRUS software after delineation of the prostate by the investigator on the TRUS image.

3. An LDI equal or superior to 1.0 should be achieved for each zone to be treated.

6.2.5 Choice of zones to be treated

The treatment guidance will be conducted in order to treat the lobe of the prostate that contains cancer lesions. Prior biopsy data will be used to determine the lobe to be treated (target treated zone).

Treatment guidance will use the enrollment biopsy results and TOOGUIDE- TRUS software.

The plan will indicate the zones to be treated.

In case of unilateral disease, focal treatment of one lobe will be applied. In case of bilateral disease (discovered at entry or during follow-up), bilateral treatment will be applied consecutively or simultaneously.

6.2.6 Approaches for Protection of adjacent tissues in Treatment Guidance

To ensure that the rectum and urinary sphincter will not receive excessive light doses, a safety margin of at least 5mm will be maintained between the light delivery fibers and:

1. the rectal wall,
2. the apex of the prostate,
3. the urethra.

6.3 TOOKAD® Soluble VTP treatment procedure

6.3.1 Overview of procedure

The VTP procedure[26] will consist of a single, 10 minute infusion of 4mg/kg TOOKAD® Soluble. The drug will be activated by laser light at 753nm, with a dose of 200J/cm, and a fixed power of 150mW/cm, given over 22min 15s and delivered using interstitial optical fibers, inserted using a transperineal route, into the prostate gland:

1. A transperineal template is used for the placement of the transparent catheters which are positioned in the prostate under transrectal ultrasound image guidance.
2. The optical fibers are then inserted into the catheters.
3. The drug infusion begins once the catheter positioning is finalized.
4. The light delivery begins immediately after the completion of the drug infusion.

6.3.2 Study medicine TOOKAD® Soluble

TOOKAD® Soluble is a powder for solution for injection, presented in 200 mg or 400 mg vials. Before administration, the product is extemporarily reconstituted with a 5% solution of Dextrose, to reach the final concentration of 10 mg/mL and the solution is kept protected from light.

After preparation of the drug, the syringes, the infusion lines and the point of injection will be protected from light until the end of the injection.

Subjects are required to fast per institutional standards before the VTP procedure.

The duration of injection will be the same for all the subjects (10 minutes). A single dose of 4 mg/kg of TOOKAD® Soluble will be administered.

6.3.3 Storage, Packaging, Dispensing, Reconciliation, and Return of Supplies

TOOKAD® Soluble will be supplied by the Sponsor as vials containing 200 mg or 400 mg of powder for solution for injection. In compliance with local laws and with Good Manufacturing Practices (GMP) boxes will be labelled in the local language in the country of administration, including at least the following information:

1. Sponsor name and address,
2. Study reference number,
3. Treatment number,
4. Name of Principal Investigator,
5. Name of drug,
6. Dose and formulation,
7. Administration method,
8. Batch number,
9. Expiry date (day/month/year) and
10. Legal notes.

The study medication will be stored in a secure area maintained at 2°C to 8°C, under the responsibility of the pharmacist. Only personnel properly informed of preparation procedures will be permitted to dispense study medication. The process for drug preparation will be under the responsibility of the study site Pharmacist. In case of temperature excursion the pharmacy will notify the Sponsor or designee within 48 hours and place the drug under quarantine until the Sponsor has given a written approval to use the drug.

All supplies shipped to site must be properly accounted for. Upon receiving study medication the pharmacist will immediately return the acknowledgement receipt to the Sponsor or the Sponsor's designee; this receipt records the signature of the person receiving the study medication and the date received.

The pharmacist responsible for dispensing the study medication will receive a drug dispensing schedule. The Investigator should keep accurate records regarding the dispensing and return of study medication and any departure from the expected dispensing or return of study medication must be recorded.

At the termination of the study the Drug Accountability Record will be completed. All study medication (used and unused), in its packaging, will be returned to the Sponsor unless written approval from the Sponsor authorizing the destruction. Unused bottles are to be kept refrigerated and protected from light until instructions from the Sponsor or the Sponsor's designee.

6.3.4 Procedures carried out in the operating-room

Light delivery catheter insertion:

Subjects will be placed in the lithotomy position and will remain in this position throughout the procedure. A Foley catheter is placed in the bladder prior to the procedure, and removed at least 6 hours after the procedure. TRUS images are used to visualize the prostate and to define the treatment guidance using TOOGUIDE TRUS.

A transperineal template is used to guide the placement of the flexible hollow introduction catheters into the prostate. These have a metal inner mandrel to aid insertion. This procedure is similar to that used routinely for high dose rate (HDR) brachytherapy of prostate cancer.

Following satisfactory positioning of the introduction catheter the metal mandrel is removed and replaced with a cylindrically diffusing optical fiber. The length of the diffusing part of the fiber is chosen according to the treatment guidance based on the ultrasound images of the prostate. Fibers are available with illuminating fiber lengths of 1 - 5 cm, in 0.5 cm increments.

Laser:

The lasers to be used for the procedure (Intermedic, Spain) are connected to the optical fibers, once the optical fibers are satisfactorily positioned within the flexible introduction catheters.

Light detection:

One light detecting probe will be placed in the rectum to ensure that the light dose is sufficiently low. The prostate is illuminated prior to drug injection and the light measured. If the light in the rectum exceeds 13 mW/cm² then the optical fibers in the prostate will be repositioned.

Drug delivery:

The infusion puncture site should be placed in a large vein at the top of the forearm. The infusion will be conducted using automatic syringes, through a fast flow peripheral line (antecubital catheter). The Sponsor will provide the study centre with the appropriate infusion devices. Infusion will be over 10 minutes. The choice for size of intravenous catheter will be left up to the discretion of the involved medical

team who will be responsible for ensuring that the catheter is flushed and working properly prior to starting infusion.

Light delivery:

The light delivery will begin once the drug infusion has ended. Light will be delivered at an energy dose of 200 J/cm with a power of 150 mW/cm over 22min 15s.

See appendix 6 “VTP procedure Book”.

6.3.5 Light Protection Following TOOKAD® Soluble Administration

Instructions for light protection following TOOKAD® Soluble administration are found in Appendix 3. In the recovery room and ward, dim general lighting should be used. Blinds should be utilised to prevent sunlight exposure and direct reading lamps will not be used. If dim lighting cannot be achieved, then local screens should be placed around the subject. If the subject reports any discomfort to the skin or eyes during hospitalisation, the general level of lighting must be reduced and extra care taken to shield both artificial and natural light.

6.3.6 Prevention of Thrombosis Following VTP

The risk of thromboembolic events is known to be increased following general anaesthesia, and especially when it is associated with pelvic surgery for cancer. Therefore, prophylactic measures will be taken to avoid such events.

The choice of the measures for the prevention of thromboembolism is left at the discretion of the investigator, as per local clinical standards [e.g., subcutaneous injection of low molecular weight heparin (LMWH), pneumatic compression devices].

6.3.7 Concomitant Medication

Previous medication (started before the screening visit) and concomitant medication (started at the screening visit or up to the last visit, whether there is continued use or not) must be identified in the subject’s medical record, including all the medication administered with TOOKAD® Soluble -VTP and in the immediate post-procedure period. These medications will be recorded on the electronic case report form (eCRF).

For each medication taken, the following information will be collected:

1. Medicine trade name (including dose and frequency),
2. Indication for which the medication was prescribed,
3. Date started and Date stopped.

6.3.8 Prohibited Concomitant Medication

1. Medications 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 and for 3 days after the TOOKAD® Soluble -VTP 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.

2. Anticoagulant drugs (e.g., warfarin) are prohibited if they cannot be stopped at least 10 days before the TOOKAD® Soluble- VTP procedure.

3. Compounds that decrease clotting, vasoconstriction, and platelet aggregation (e.g. aspirin) should be stopped at least 10 days before and for 3 days after the TOOKAD® Soluble- VTP procedure.

4. OATP1B1 and OATP1B3 transporter substrates: 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 (e.g.statins) cannot be ruled out. The use of medicinal products that are substrates of OATP1B1 or OATP1B3 for which concentration-dependent serious adverse events have been observed should be avoided on the day of TOOKAD® Soluble infusion and for at least 24 hours after administration. Co-administration should be done with caution and close monitoring is recommended.

5. A list of prohibited medications is provided in Appendix 10.

6.3.9 Laser storage

The lasers (Intermedic) and a user manual will be supplied by the Sponsor. The lasers will be stored in an appropriate locked room, under the responsibility of the site Investigator. The Sponsor will provide a qualified, experienced laser operator to attend all TOOKAD® Soluble- VTP procedures and train assigned on-site personnel in the use of the laser, until this training has been completed and the site has the required expertise to operate the laser.

6.4 Elements of Study Process – Study visits

6.4.1 Visit 1 (V1) and screening period

Apart from the patient's file review and information of the patient about the study, no study related procedure should be done or prescribed before the patient has signed the Patient Informed Consent Form (PICF).

1. Review of existing prostate biopsy
2. Review inclusion/exclusion criteria
3. Informed consent
4. Medical history
5. TNM staging
6. Digital rectal examination
7. Prostate volume
8. IPSS and IIEF questionnaires
9. Concomitant medication, and review of prohibited medication (see Appendix 10)
10. Clinical examination including vital signs (blood pressure and pulse rate)
11. Blood sample for laboratory evaluations including PSA or review of existing laboratory results if available in the patient file before he was considered for inclusion in the study, and done not more than 4 weeks before visit 1.
12. MRI

6.4.2 Visit 2 (V2): TOOKAD® Soluble VTP procedure

Subjects will come to the unit on the day of the procedure, having fasted per institutional standards in preparation for anesthesia. After the TOOKAD® Soluble- VTP treatment, they will remain in the clinical unit under medical and nursing supervision for at least 6 hours after TOOKAD® Soluble infusion. The subject will be kept under medical surveillance in a dimmed room for at least 6 hours after the procedure and may be discharged in the evening of the procedure day. Depending on the duration of the anaesthesia and the patient condition, the investigator can decide to keep him hospitalised overnight. In this case, the patient may be discharged in the following morning. Further need for inpatient based hospital care will be based on the patient's condition and medical needs as determined by the treating physician. Post-procedure hospitalization is expected to vary from approximately 6 to 24 hours. If for any reason other than those listed above (i.e., distant home) the investigator decides to keep the patient overnight, such

reason is to be recorded in the CRF, and a mention is to be made that the patient could have been discharged in the evening of the procedure day.

Prior to Anaesthesia:

1. Concomitant medication
2. AEs recording
3. Vital signs (blood pressure, pulse rate and body weight)
4. Blood collection for laboratory testing and PSA testing

After anesthesia has been induced, anesthetic monitoring is to be done according to institutional clinical practice guidelines. Patients are to be placed in the lithotomy position and to remain in this position during the procedure. During the procedure, the patient's skin and eyes are to be protected from the operating room surgical lights with opaque drapes.

After the VTP procedure, the following procedures and assessments are to be made:

1. Recording of adverse events (AEs)
2. Performance of clinical examination
3. Assessment of concomitant medication
4. Blood samples for laboratory and PSA testing 4 to 6 hours following the procedure
5. Removal of catheter

The subject is then discharged from the hospital, unless there are medical reasons that require prolonged hospitalisation.

6.4.3 Visit3 (V3): Day 7 +/- 2 days

Subjects will come to the unit seven days after the procedure for the following assessements:

1. Recording of AEs
2. Assessment of concomitant medication

6.4.4 Visit 4 (V4): Month 1 (±1 week)

1. The procedures for this assessment are:Blood collection for laboratory testing and PSA testing
2. Recording of AEs
3. Collection of IPSS and IIEF questionnaires
4. Assesment of concomitant medication

6.4.5 Visit 5 (V5): Month 3 (±2 weeks)

The procedures for this assessment are:

1. Multiparametric MRI of the prostate with contrast. The procedure for this MRI is described in Appendix 2
2. Blood collection for laboratory and PSA testing
3. Performance of prostate biopsy
4. Recording of AEs
5. Assessment of concomitant medication
6. Collection of IPSS and IIEF questionnaires

6.4.6 Visit 6 (V6): Month 6 (±2 months)

The procedures for this visit are:

1. Blood collection for laboratory testing and PSA testing
2. Recording of AEs
3. Assessment of concomitant medication
4. Collection of IPSS and IIEF questionnaires

6.4.7 Visit 7 (V7): Month 12 (±2 months)

The procedures for this visit are:

1. Blood collection for laboratory and PSA testing
2. Recording of AEs
3. Assessment of concomitant medication
4. Collection of IPSS and IIEF questionnaires
5. Performance of prostate biopsy
6. MRI

6.4.8 Visit 8-10 (V8-V10) Months 24 (± 3 months), 36 (± 3 months), 48 (± 3 months)

1. Blood collection for laboratory and PSA testing
2. Recording of AEs
3. Assessment of concomitant medication
4. Collection of IPSS and IIEF questionnaires

5. Performance of prostate biopsy, as indicated per institutional standard of care
6. MRI, as indicated per institutional standard of care

6.4.9 Visit 11 (V11) Months 60 (± 3 months) – End of study visit

1. Blood collection for laboratory and PSA testing
2. Recording of AEs
3. Assessment of concomitant medication
4. Collection of IPSS and IIEF questionnaires
5. Performance of prostate biopsy, as indicated per instutional standard of care
6. MRI, as indicated per institutional standard of care

6.4.10 Additional Visits

A single re-treatment of lobes found positive for cancer at 3-months follow-up is allowed.

Those additional treatments will be performed in the same conditions as for the first VTP procedure (section 6.4.2.). The schedule of visits will remain unchanged and the whole study duration will be sixty months.

6.4.11 Post-procedure or follow-up assessments

Based on the results of post-procedure or follow-up assessments, or upon decision by them or their clinician, patients may at any time decide to undergo additional radical therapy.

7 OUTCOMES ASCERTAINMENT

7.1 Prostate biopsy

All subjects will undergo biopsy at 3 and 12 months according to protocol. The need for subsequent biopsy beyond 12 months will be at the discretion of the investigator according to standard of care. All biopsy procedures will consist of a transrectal ultrasound guided prostate biopsy with a minimum of 12 cores and include both lobes of the prostate gland. Any suspicious volumes meeting PIRADS (version 2) criteria of level 4 or 5 found on MRI will be targeted with at least 2 cores taken from each suspicious lesion. Patients will undergo pre-biopsy preparation using standard of care practices for the institution that should include the use of peri-procedural antibiotics. Patients who fail to receive antibiotics for the biopsy procedure will be considered a violation.

Anatomopathological reports will include:

1. The number and length of cores taken,

2. The number and the location of cores with cancer,
3. The cancer core length (CCL) which is linear millimeters of cancer on each core and the percentage of cancer on each core,
4. The Gleason grading of each core.

7.2 Patients' questionnaires on erectile dysfunction and urinary symptoms

The following questionnaires will be applied to all patients to assess erectile function and urinary symptoms at entry and at months 1, 3, 6, 12, 24, 36, 48 and 60:

- IIEF-15 for erectile function

The International Index of Erectile Function (IIEF) relates to the following areas: confidence in erection; erection sufficient for penetration; maintaining of erection; difficulty to maintain erection for completion; satisfactory intercourse. Subjects will be asked to give their response to each of the areas using a 6-point scale (0=no sexuality, 5=best response).

- IPSS for lower urinary tract symptoms

The International Prostate Symptom Score (IPSS) is an 8-question questionnaire focused on urinary symptoms with one general question about urinary symptoms. The questions relate to the following areas: sensation of bladder emptying; frequency of urination; stops when urinating; difficulties to postpone urination; urinary steam; beginning of urination; night urination. Subjects will be asked to give their response to each of the areas using a 6-point scale (0=none or normal, 5=worse response).

These questionnaires will encompass the consequences of all treatments, including additional radical therapy potentially used by patients. Scores for each one of the scales will be calculated regardless of failure or not, and additional treatment or not.

8 ADDITIONAL ASSESMENTS

8.1 Assessment of Clinical Signs of Suspected Rectal, Urethral or Bladder Injury

For suspected rectal, urethral or bladder injury, imaging studies should be performed as appropriate, with direct visualisation (cystoscopy and proctoscopy) performed when clinically necessary. In cases where such procedures are performed during the time of the protocol, photographic documention of findings should be obtained when possible and maintained with the patient's records with de-identified copies made available upon request to the Sponsor. For subjects with confirmed injury, standard clinical care including referral to a specialist for corrective procedure and/or surgery will be performed. Clinical signs should be followed up at each subsequent study visit until resolution of the injury has been confirmed.

8.2 Post Treatment MRI

Prostate MRI

MRI of the pelvis and prostate gland will be performed at 3 months and 12 months following VTP treatment. Additional MRI may be performed at the discretion of the investigator up to 60 months. Results from these studies are used to confirm expected treatment effects to the prostate gland as well as evaluate for any extra-prostatic tissue changes that may be associated with side effects and find any suspicious lesions within the prostate. Any suspicious volumes meeting PIRADS (version 2) criteria of level 4 or 5 found on MRI will be targeted with at least 2 cores taken from each suspicious lesion. Additional clinically actionable findings identified on MRI will be left to the discretion of the treating physician. Lymph nodes that are 15 mm in diameter or smaller in size will be considered negative by convention although may be biopsied at the discretion of the physician. Lymph nodes greater than 15 mm in diameter will be considered suspicious by convention and will require biopsy confirmation of cancer to be classified as metastases.

8.3 Laboratory Assessments

Choice of the laboratory

A local laboratory will be used for safety biological parameters and PSA testing.

Laboratory examinations

The following laboratory tests should be prescribed at Visit 1 and their results should be available for eligibility assessment prior to the VTP procedure. If similar laboratory tests are available in the patient file before the patient is considered and approached for his entry in the study, the results of these test can serve as the eligibility assessment and do not need to be repeated, provided they have not been done more than 4 weeks before visit 1.

At any time during the study, for safety reasons, and when in the patient's best interest, additional tests may be performed at the discretion of the Investigator.

If one of the result of the laboratory tests (eg PSA levels) done after consent signature do not meet the inclusion/exclusion requirements, it can be repeated at the discretion of the investigator, but not more than twice.

Screening (V1) blood tests:

- Standard hematologic tests
- Standard blood chemistry tests
- Standard Blood Coagulation Tests

- Additional inclusion blood tests
- PSA

Blood tests to be taken during the during Visit 2 both before and after the TOOKAD® Soluble VTP procedure as well as taken 1, 3, 6, 12, 24, 36, 48 and 60 months after the VTP procedure:

- Standard hematologic tests
- Standard blood chemistry tests
- PSA

Standard hematologic tests:

Hemoglobin, Red cell count, M.C.V., Hematocrit, M.C.H., White cell count, Differential white cell count (%), Platelet count.

Standard blood chemistry tests:

Sodium, Potassium, Chloride, Bicarbonate, Calcium, Creatinine, Urea, Glucose, Total Protein, Albumin, Alkaline Phosphatase.

Standard Blood Coagulation Tests:

INR (pro-time), aPTT.

Additional inclusion blood tests:

Alanine Aminotransferase (ALAT/SGPT) and Aspartate Aminotransferase (ASAT/SGOT)

PSA:

Prostate Specific Antigen

9 SAFETY EVALUATIONS

Safety assessments include adverse events, anaesthetic monitoring and laboratory assessments.

9.1 Definitions

The term “adverse event (AE)” is predominantly used for defining adverse events which occur in connection with medicinal drug product use. The term “adverse event (AE)” may also be used for defining adverse events which occur following the use of a device or following a procedure where the drug or

device is used. Within this protocol, the term "adverse event (AE)" is being used for drug, device or procedural occurrences.

Adverse Event (AE) (Drug)

Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Unless stated otherwise by the investigator, any clinically significant abnormality discovered for a screening assessment required by the protocol will be considered as medical history and not as an AE.

Adverse Event (AE) (Device)

Any untoward medical occurrence, unintended disease, undesired event or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects/patients, users (healthcare professionals) or other persons whether or not related to the investigational medical device including events related to the investigational device

Device Deficiency

Any inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Procedural events

Any untoward medical occurrence, unintended disease, undesired event or injury or any untoward clinical signs that arises as a result of procedures involved (any procedure in the clinical investigation plan).

For users or other persons, this is restricted to events related to such procedures including anaesthesia, the placement of the fibers or anything else not directly due to the use of the Laser device or drug occurring at the time of the VTP.

Serious Adverse Event (SAE)

Within this protocol, a serious adverse event is any adverse event regardless of causality that meets at least one of the seriousness criteria listed below:

1. Led to a death,

2. Led to a serious deterioration in health that either:
   - resulted in a life-threatening illness or injury, or
   - resulted in a permanent impairment of a body structure or a body function, or
   - required in-patient hospitalization or prolongation of existing hospitalization, or
   - resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect,
4. Is considered a medically significant event that lead, could have lead, or could lead directly or indirectly to death or severe health impairment of volunteers, users, or other persons if action was not taken to prevent this (including surgical intervention).

NOTE: An SAE may include a report of malfunction of the device such that it has to be monitored more closely or temporarily or permanently taken out of service.

9.2 Adverse Event Monitoring

Any device deficiency that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate must be reported. Each subject must be carefully monitored for AEs. This also includes abnormal laboratory values. An assessment must be made of the seriousness, severity and relationship to the administration of the study drug and/or the study device(s) and/or the technical procedures of the study. For the purpose of this study, the procedure includes anaesthesia, the insertion, positioning and removing of the catheters and urinary catheterisation of the patient.

The follow-up of patients will be undertaken until 5 years (60 months). It will encompass ALL AEs events occurring during that period, including any occurring after the initiation of additional prostate cancer treatment.

The Investigator is required to question the subject about AEs and intercurrent illnesses since their last visit and must register the information in the subject's medical records. The questions should be generalised and the presence or absence of specific AEs should not be solicited from subjects. The onset and end dates, severity and relationship to study drug must be registered for each AE, as well as outcome, action taken and seriousness (see Section 9.1 for definition).

Subjects experiencing AEs will be monitored by the investigator. All AEs should be followed until satisfactorily resolved or stabilised. Any action taken and follow-up assessments must be recorded in the subject's medical record. Results from follow-up assessments should be filed with the subject's source documentation.

At the end of the study, the investigator will ensure that the end date (if applicable) and any sequelae of all related AE have been fully documented and followed until resolution. If appropriate, the final relationship of AEs to the study drug, device or procedure will be re-assessed. Any ongoing AE, including out of range safety laboratory parameters, will be followed until resolution or no further improvement can be expected. Appropriate action may be taken as judged clinically necessary.

9.3 Documentation of Adverse Events

AE collection will begin after consent has been obtained and continue until the final visit. Every AE or symptom will be recorded in the CRF and will include:

1. nature (brief description)
2. date and time of onset
3. date and time of resolution
4. seriousness (see Section 9.1 for definition)
5. relationship (unrelated, unlikely, possible, probable, or very likely) to the study drug estimated by the investigator
6. if study-related:
   - study drug-related
   - study device-related
   - study technical procedure-related
7. action taken
8. outcome

On the basis of the occurrence and intensity of AEs, coupled with results of any other observations, the Investigator, at his discretion and following discussion with the Sponsor, may decide to withdraw a subject or prematurely end the study for reasons of clinical safety. The date of such termination will be recorded and appropriate treatment instituted at the discretion of the investigator or sub-investigator.

9.4 Serious Adverse Events Reporting

1. AE collection will begin after consent has been obtained and continue until the final visit.
2. All SAEs including laboratory tests abnormalities fulfilling the definition of seriousness and occurring during the clinical trial from the point of signing informed consent to final visit, or within 28 calendar days following the study treatment whichever is the later must be reported immediately (within 2 days of knowledge of the SAE by the Investigator) to the Pharmacovigilance CRO who is in charge of the study pharmacovigilance. A causality assessment will be applied for each event documented. Note that symptoms and signs (such as laboratory abnormalities) that are features of a recognized adverse event should

not be reported separately; i.e. pneumonia which is associated with cough, fever and raised white cell count should only be reported as pneumonia with the signs and symptoms as supporting information.

3. Life-threatening or fatal SAEs regardless of relationship to study drug, study device or study procedure must be reported to the Pharmacovigilance CRO by the investigator (or sub-investigator) within 24 hours of knowledge of the event.
4. The report of an SAE should be made by transmitting the Report Form (as provided in the investigator Site File) to the Pharmacovigilance CRO. The investigator must provide at very least the following information: trial number, subject's initials, date of birth, and patient number, date of treatment, nature of the AE and Investigator's causality assessment (related yes/no to study drug, device or and/or procedure).
5. The report of any SAE must always be confirmed by a written SAE form completed as fully as possible and signed by the investigator. This report must be sent to the Pharmacovigilance CRO within 2 days of the event occurring.
6. The investigator will be informed by the Sponsor of any additional individual national reporting requirements for SAEs applicable in their country and the sponsor will train the investigator to be in compliance with such requirements.
7. The cause of death of a subject in a clinical trial should be reported as an SAE. The only exception is sudden death (when the cause of death is unknown), which is reported as an SAE with death as the outcome.
8. Progression of patient's prostate cancer which is identified as a study end point should not be reported as an SAE unless the investigator assesses that this progression is related to the study procedure or study drug. If any SAE occurs at any point after the study follow-up period, which is considered by the investigator to be related to the study drug or study procedure, this should be reported to the Sponsor/Sponsor representative.
9. If a subject participating in this study requires an extra period of hospitalisation for social reasons either at the start or end of a treatment, this should not be considered a hospitalisation justifying an SAE report.
10. Attendance at hospital that does not require an overnight stay or is for tests only should also not be considered a hospitalisation justifying an SAE report.

Note: medical and scientific judgment should be exercised to decide whether expedited reporting is appropriate in other situations.

All SAE drug reports which meet the reporting criteria will be submitted by the Sponsor to the relevant national or international authorities according to the national regulations, directives and timescales in

force in the different countries where the study is conducted. A separate document will be produced by the Pharmacovigilance CRO which details all reporting requirements.

9.5 Device Reports (AEs)

During the course of the study, AEs which may be attributable to the use of these devices may occur. All events should be collected regardless of whether the event was causally related to the device or not.

Any SAE device reports should be captured using the SAE report form, and submitted to the Pharmacovigilance CRO following the same timelines and procedure as for SAE drug reports. All SAE device reports will be submitted by the Sponsor to the relevant national or international authorities according to the national regulations, directives and timescales in force in the different countries where the study is conducted. A separate document will be produced by the Pharmacovigilance CRO which details all specific reporting requirements.

9.6 Pharmacovigilance contact information

The same communication system is used for reporting drug/device/procedure-related SAEs forms. All forms can either be scanned and e-mailed, or faxed.

First route of transmission	**Email: steba@primevigilance.com**
Second route of transmission	**Fax: +44 (0) 1483 431 831**

10 STATISTICS

10.1 Sample size

The trial sample size was calculated to achieve 80% power to reject the null hypothesis H0="r≤70%", using a one-sided exact binomial test with 5% alpha risk.

From historical clinical data, the true response rate is expected to be greater than 90%. However, to remain conservative the true response rate could only be estimated from localized intermediate-risk prostate cancer patients patients who underwent the TOOKAD Soluble procedure and for whom biopsies were available after 12 months. Using these conservative estimates we identified a true response rate is greater than 83.6% with >80% posterior probability (assuming a beta-binomial model).

Using this conservative choice for true response rate r=83.6% a minimum of N=44 patients with fully evaluable data is required.

10.2 Planned statistical methods

10.2.1 Overview

A statistical analysis plan (SAP) describing the detailed statistical analysis will be provided as a separate signed document.

The statistical analysis will consist of reporting of individual data listings, providing descriptive statistics and graphs for all parameters of interest, and applying the statistical test of the primary analysis.

10.2.2 Descriptive analysis

10.2.2.1 Patient characteristics:

1. Age
2. Ethnic origin
3. Country
4. Medical/surgical history including pre-treatment events
5. Previous and concomitant medication
6. Histological data: proportions of unilateral and bilateral disease, number of cores involved
7. Morphometric data: prostate volume

10.2.2.2 Treatment modalities:

1. Number of fibers and energy applied
2. LDI achieved
3. Adherence to treatment guidance and reasons for changes

10.2.2.3 Descriptive statistics

Descriptive statistics (number, mean, standard deviation, median, quartiles, minimum and maximum) will be calculated for quantitative variables; frequency counts and cumulative frequencies (if appropriate) by category will be given for qualitative variables. For measurements that are repeated over time (e.g. PROMs and QoL), descriptive statistics will be provided at all measurement times and summary statistics will be plotted over time. Two-sided 95%-confidence intervals will be given where appropriate. These intervals will be two-sided and will have 95% coverage.

10.2.2.4 Intention-to-treat, per protocol and safety populations

All descriptive statistics will be shown on all patients enrolled in this study, for whom CRF at entries are available irrespective of protocol deviations (**intention-to-treat population**). Safety data will be analyzed using all patients who have received any amount of TOOKAD® Soluble or have started any part of the VTP procedure, including anesthesia (**safety population**).

Descriptive statistics will also be shown using all patients who comply with the study protocol (**per-protocol population**). The per protocol population of efficacy will consist of all patients who:

1. complied with the protocol for inclusion criteria and exclusion and follow-up,

2. received the appropriate dose of TOOKAD® Soluble, LDI and energy delivered and underwent the VTP procedure, receiving the ascribed dose of TOOKAD® Soluble and light,
3. had no major protocol deviations.

10.2.2.5 Drop-outs and censored patients

All subjects who withdraw from the trial before the VTP procedure will be considered as drop-outs. Every effort will be made to minimize dropouts.

Eligible subjects who undergo additional radical therapy (surgery or radation) after the VTP procedure or receive medical therapies (hormone or chemotherapies) will be kept in the intention to treat population but will be excluded from the per protocol population.

10.3 Analysis of primary endpoint

The primary efficacy variable is the result of the Month 12 biopsy, in which success is defined by absence of detectable Gleason grade 4 or 5 prostate cancer in any given biopsy.

The primary endpoint will be analysed as a dichotomous outcome, i.e., success (absence of any histology result positive for Gleason 4 or 5 prostate cancer at 12 months) or failure (presence of at least one result positive for Gleason grade 4 or 5 prostate cancer at 12 months).

A descriptive analysis of the month-3 biopsies will be conducted.

10.4 Secondary efficacy endpoints

10.4.1 Definitions

Secondary endpoints are defined as:

- Binary response to treatment defined as the absence of any Gleason grade 4 or 5 biopsy on or before months 24, 36, 48 and 60. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of gleason grade 4 or 5, the subject will be considered to have responded;
- Binary response to treatment defined as the absence of any Gleason grade 4 or 5 biopsy on or before months 12, 24, 36, 48 and 60 in the treated lobe. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of gleason grade 4 or 5, the subject will be considered to have responded;

Samples obtained from prostate biopsy procedures will undergo routine processing and examination by the department of pathology at the treating institution. Absence of any any Gleason pattern 4 or 5 prostate cancer will be considered negative as will the findings of atypia or prostatic intraepithelial neoplasia.

- Binary response to treatment defined as the absence of any prostate cancer on biopsy on or before months 3, 12, 24, 36, 48 and 60. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of any cancer, the subject will be considered to have responded;;
- Binary response to treatment defined as the absence of any prostate cancer on biopsy on or before months 3, 12, 24, 36, 48 and 60 in the treated lobe. If a subject is retreated following a positive biopsy at 3 months and subsequent biopsy shows absence of any cancer, the subject will be considered to have responded;

Samples obtained from prostate biopsy procedures will undergo routine processing and examination by the department of pathology at the treating institution. Absence of gradable prostate cancer will be considered negative as will the findings of atypia or prostatic intraepithelial neoplasia.

- Changes in biopsy result between 3, 12, 24, 36, 48 and 60 months after the procedure.

Biopsy results obtained at 3 , 12, 24, 36, 48 and 60 months will be compared in each patient to look for change in pathologic findings of gradable cancer between the time points.

- Patients' reported outcome measures (PROMs) impairment: urinary symptoms using IPSS and erectile functions using IIEF prior to treatment beginning and then 1, 3, 6, 12, 24, 36, 48 and 60 months after completing treatment

Quality of life is assessed using validated questionnaires. The IPSS comprises seven questions on the urinary symptoms plus one general question about the QOL related to urinary symptoms, whereas the IIEF comprises 15 questions. For both questionnaires, patients self-rate their responses: for the IPSS, using a six-point scale where 0 indicates 'none' or 'normal', whereas 5 indicates the worst response; for the IIEF, using a five- or six-point scale where 0 indicates 'no sexual activity', and 5 indicates the best response (questions 1 to 10), or where 1 indicates the worst response and 5 the best response (questions 11 to 15).

- Rate of adverse events following treatment

As described in section 9.1, adverse events will be recorded and reported descriptively. Events will be annotated and graded according to National Cancer Institute Common Toxicity Criteria version 4.03.

- Severe prostate cancer-related events: cancer extension to T3, metastasis or prostate cancer-related death

Stage progression to T3 disease (extracapsular extension or seminal vesical invasion), metastasis or cancer-related death will be assessed based on tissue confirmation with biopsy or post-mortem evaluation. Radiographic evidence of suspicious findings will not be utilized unless confirmed with tissue sampling.

- Use of secondary cancer therapies following VTP treatment

Patients who proceed to additional therapies for prostate cancer treatment such as radiation, surgery, hormone or chemo therapies will be documented . Adjunctive surgical or medical therapies that are not intended as cancer treatments but for management of post-treatment related events will be recorded under adverse event reporting and graded appropriately.

- Serum PSA measurements in ng/mL.

Patients blood will be drawn and PSA level determined at 1, 3, 6, 12 months and annually thereafter. Changes from baseline will be determined.

10.4.2 Analysis of secondary variables

Secondary variables will be analyzed using standard descriptive statistical methods listed in section 10.2.

10.5 Statistical analysis of safety

The safety and tolerability assessments will be evaluated using the following data:

1. Outcome of adverse events
2. Clinical examination

10.5.1 Analysis of adverse events

Distinctions will be made between the adverse events not related to the study treatment, the technical procedure or the study device, and those related to any of the above.

Numbers and frequencies of AEs will be tabulated and the proportions of patients exhibiting each AE will be displayed. The adverse events will be classified according to the MedDRA nomenclature. The treatment-emergent adverse events (which happen or worsen after the first study drug intake) will be summarised by System Organ Class (SOC) and preferred term. In addition, the adverse events will be classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) which is a safety endpoint of the study. Tabulations will also be made for the System Organ Class (SOC, current MedDRA version), intensity, relationship, seriousness, and attribution corresponding to each AE. Separate tabulations will be made for SAEs.

The treatment-emergent adverse events (which occurred or worsened after the first study drug intake) will be summarised by primary SOC system and preferred term.

For pre-treatment events listings will be provided. For medical/surgical history and additional examinations listings will be provided.

11 STUDY MONITORING - ACCESS TO SOURCE DATA

11.1 Definition & purpose

The Sponsor monitor or designee is responsible for establishing the schedule and procedures to be followed for monitoring this study. Monitoring will be made at regular intervals during the study. Prior to the beginning of this study, the Investigator will be informed as to the anticipated frequency of the monitoring visits. In addition, the Investigator will receive due notification prior to each monitoring visit during the course of the study.

The purpose of these visits is to verify:

1. The informed consent process is properly documented
2. The reporting of AEs and all other safety data
3. Adherence to the protocol
4. Maintenance of required regulatory documents
5. Study supply accountability
6. Completeness and accuracy of the CRF data and other data submitted

At each visit, the investigator will be expected to cooperate with the Sponsor's representative(s) for the review and verification of all CRFs, the drug supply and inventory records and any additional records that may have been previously arranged.

11.2 Source Data

The data corresponding to the VTP procedure will be recorded in a specific document provided by the Sponsor (VTP report form) and will be considered to be source data. The VTP report form collects all the technical information (power, energy, diffuser length, etc.).

If the study site uses electronic subject files then the participant' records will be printed, dated and signed by the Investigator. These records will be kept in the subject's study file and will be used for source data verification.

11.3 Pre-Study training

Pre-Study Visit

At the pre-study visit, the Sponsor or his designee will ensure that the investigator has the technical means and the staff to carry out the study with regard to availability, subject recruitment, facilities and environment.

Study initiation

The Sponsor or Sponsor's representative will provide training at study site on the study procedures and assessments prior to the start of the study; this training will occur as an individual site initiation visit.

Prior to the start of the study, the following information must be sent by the site to STEBA:

1. Protocol and financial agreement signed by all parties
2. Written approval from the IECs/IRBs
3. Curriculum vitae of the Investigator
4. Appropriate regulatory documentation.

11.4 Study Monitoring Visits

A study monitor will ensure the monitoring of the study at regular intervals.

At each monitoring visit, the CRFs will be 100% verified against the source documents to ensure adherence to the protocol and compliance of the site to the regulatory requirements. The monitor will also review the study medication records, regulatory documents and correspondence, perform study supply accountability and will periodically inspect the facilities to ensure that the sites study documentation, personnel and facilities remain adequate for the duration of the study. The monitor shall have access to the source documents and other information needed to ensure investigator compliance with the clinical investigation plan and applicable rules and regulations, and to assess the progress of the clinical investigation.

The monitor will address all the errors, omissions and issues with the Investigator and/or other appropriate study personnel, and will ensure that the appropriate corrective action is taken.

11.5 Study Termination Visit

At the end of the study, STEBA will be provided with:

1. Completed CRFs
2. Used and unused medications and remaining packaging. Unused bottles are to be kept refrigerated and protected from light until instruction from the Sponsor or the Sponsor's designee. They will be returned to the Sponsor unless written approval from the Sponsor authorizing the destruction.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Good Clinical Practice

The study will be conducted in compliance with Good Clinical Practice as stated in the ICH Harmonised Tripartite Guidelines (CPMP/ICH/135/95), the declaration of Helsinki (see Appendix 1) all applicable state and local regulations.

12.2 Standard Operating Procedures

The study will be conducted according to pre-established written Standard Operating Procedures (SOP) of the Sponsor or its agents. The Quality Assurance personnel of the Sponsor or the Sponsor's designee may audit the clinical investigator's site at any time during the study. The investigator and his/her team must be available during such audits, allowing auditors to access to the technical site, study material, source data and subject's file. The subject's anonymity must be safeguarded and data checks during the audits must remain confidential.

12.3 Protocol Amendment Procedure

With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted without the documented approval of the Sponsor.

The IRB/IEC which granted the original approval for the study must be notified of all changes in the protocol and must provide documented approval of any change or deviation which may increase the risk to the subject and/or which may adversely affect the rights of the subject or validity of the investigation.

This stipulation does not apply to those changes made to reduce discomfort or potential risk to the subjects.

In the event of any emergency, the investigator will perform all medical procedures which he deems appropriate. However, all such procedures must be promptly reported to the Sponsor.

12.4 Anonymity of Subject Identification

Each subject selected in the study will be assigned a sequential 'selection number'. The subject selection number will consist of seven digits, which will reflect ISO code of the country, the centre number and the subject number in the centre. The first subject selected for screening in a country ISO code XXX in a centre 01 will be subject number XXX-01-01. Additional subjects will be assigned sequential numbers: XXX-01-02, XXX-01-03, etc. This subject number is captured in the CRFs.

This 'selection number' differs from the treatment number(s) that will be assigned and reported in the CRF on the day of the VTP procedure.

If a subject is not eligible to receive the treatment and is considered a screen failure, the subject selection number may not be reassigned.

12.5 Subject's Written Information and Participation Agreement

The risks and benefits of participating in the study will be explained to each potential subject prior to entering the study. The informed consent will be written in a language style readily understood by the subject. The informed consent must be approved by the IRB/IEC prior to the initiation of the study, the performance of any study procedure and the dispensing of any study medication. The Principal Investigator or his/her designee must obtain a signed Informed Consent Form for each subject. Receipt of the signed Informed Consent Form will be documented in the CRF and the original will be retained by the Investigator. A copy of the signed Informed Consent Form will be given to each subject. If the Informed Consent Form is amended during the course of the study, subjects will be asked to renew its consent to the updated consent form and given a signed copy.

12.6 Confidentiality of Trial Documents and Subject Records

The information in this protocol and any further documentation contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations.

In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them.

Subject's identity and personal data will be processed for this study and considered as strictly confidential. None of this personal information will be revealed in study documents assigned to third people or intended for publications. For legal requirements, any medical records needed for this study that identify the subject by name will be available to the employees and agents of the Health Authorities or any other governmental or regulatory authorities. This information will also be available to authorized study representatives from the Sponsor of this study.

13 ETHICS

The study will be conducted in accordance with the Declaration of Helsinki and its most recent amendments and in compliance with Good Clinical Practice (GCP). The informed consent document(s), any protocol amendments and any other appropriate study-related documents will be reviewed and approved by the required independent ethics committee(s) (IEC) and/or institutional review board (IRB) before implementation.

Informed consent will be obtained prior to the conduct of any study-related procedures.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Handling

14.1.1 Case Report Forms

The Sponsor or designee will provide an EDC (Electronic Data Capture) system to allow data entry by site users.

Each member of the site will be assigned a username, a personal login and a password to enter into the EDC system.

The investigator will be responsible for the timeliness, completeness and accuracy of the information in the eCRF (Electronic Case Report Form).

Data will be entered according to the chronological sequence provided for in the eCRF.

All study-specific source data must be maintained on-site, kept in a file per subject.

Changes to information in the source documents will be initialed and dated and reason for change documented by the person making the change.

Copies of de-identified crucial source data will be delivered to the Sponsor. Such crucial source data includes copies of all reports (VTP Report Form, TOOGUIDE TRUS report, …), laboratory reports and other relevant documents. In these cases, the subject's identification will be kept confidential and will be limited to initials and subject identification number in the Study.

14.1.2 Data Accrual and Entry

The data will be entered by the Investigator or his/her delegate into the eCRF on an ongoing basis, ensuring all relevant items are completed, there is no missing data and that all data entered are consistent with the source documentation.

Data will be entered according to the data entry instructions provided.

The data will be electronically verified through use of automatic checks during data entry, SAS programmed edit checks to check complex conditions (if any) and data monitoring.

Data correction will be made by site users.

An audit trail will identify the person entering/correcting the data, date and time of data entry and reason for correction.

14.1.3 Coding

Any previous medication (started before the screening visit) and concomitant medication (started at the screening visit or up to the last visit) will be encoded by using the current version of the WHO drug dictionary and medical conditions will be encoded by using the current MedDRA version.

14.1.4 Data Transfer

Final validated data will be recorded in SAS® data sets and sent to the Sponsor.

14.1.5 Final Report

A final study report will be written in English. The report will give full experimental details of the clinical and analytical phases of the study.

The reports will comply with all the requirements and recommendations described in guidelines ICH E3.

14.2 Retention of Study Records

The investigator is ready to receive and cooperate with any auditor designed by the Sponsor to ascertain the performance of the study according to ICH GCP (17, 18, 19, 20, 21).

Archiving will be carried out at the clinical sites in an appropriate room designed for record retention. This room is locked around the clock, and includes fire detection monitoring.

The investigator will retain originals of the approved project protocol, subjects' participation agreements, relevant source documents will be kept per institutional guidelines and GCP and all other supporting documentation related to the project. He/she must make these files available for inspection by an authorized representative of the Sponsor or the regulatory authorities upon reasonable request. Complete CRFs have to be collected by the Sponsor at the end of the study.

All study-related records, including source documents, CRFs, and regulatory documents, must be retained as outlined in the ICH guideline for Good Clinical Practice. These documents should be retained for a longer period if demanded by regulatory requirements or by an agreement with the Sponsor.

The on-site Investigator is responsible for the retention of all study documents for the appropriate period, and must inform the Sponsor in writing of any change in the status of these documents.

The Sponsor will inform the Investigators in writing when these documents no longer need to be retained.

15 FINANCING AND INSURANCE DOCUMENTATION

Steba Biotech S.A. insurance contracts will cover the study.

16 PUBLICATION POLICY

The Sponsor or its designee will submit an ICH-compliant clinical study report to the Primary Investigator at the conclusion of the study. The contents of this report will include: study objectives, methods (including any deviation from the study protocol), evaluation of the study results, observations by the Primary Investigator regarding the value of the study drug, and a discussion of all AEs with interpretation by the Primary Investigator regarding study drug involvement.

All information concerning the tested drug and the Sponsor's operation, such as patent applications, formulae, manufacturing processes, basic scientific data and formulation information supplied by the Sponsor and not previously published are considered confidential, shall be not disclosed and shall remain the sole property of the Sponsor. The investigator agrees to use such information only within the completion of the study and will not use it for other purposes without prior written consent from the Sponsor.

It is understood by the Investigator that the information from the clinical study will be used by the Sponsor in connection with the development of the tested drug, and therefore may be disclosed as required to other clinical Investigators or to government agencies. In order to allow for the use of the information derived from the clinical studies, it is understood and agreed that there is a commitment to provide the Sponsor with complete test results and all data developed in the study. The investigator further recognizes that the disclosure of such confidential information may destroy the commercial value of the tested drug.

Disclosure of the results and all data developed in the study by the investigator for publication will not be unreasonably withheld by the Sponsor except as required for patent protection. Where the Protocol is part of a multicentre study, the investigator agrees to withhold publication or presentation of data until the date of the publication or presentation by the Sponsor of the multicentre data in full.

The information in this and any further documentation contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations.

In any event, the individuals to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them.

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