Sponsor:	Steba Biotech SA
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
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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
CRF	Case Report Form
CTC	Common Terminology Criteria
ECG	Electrocardiogram
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
LDI	Light Density Index
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OC	Observed Cases
PP	Per Protocol
PSA	Prostate Specific Antigen
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TNM	Tumor Node Metastasis
TRUS	Trans Rectal Ultrasound
VAS	Visual Analogue Scale
VTP	Vascular-Targeted Photodynamic therapy
WHO	World Health Organization

Introduction

The purpose of this statistical analysis plan (SAP) is to provide an analytic framework, which addresses analyses in support of the protocol objectives. This analysis plan is based on the protocol of the PCM204 study as protocol version 6.0 dated 1st October 2018 (MSKCC IRB# 17 070(2)).

Study Objectives, endpoints and Design

Objectives

Primary objective

The primary objective of the study i sis to evaluatefortheabsenceofbiopsydetectableGleasongrade4or5 prostatecanceron12- month, post-treatment biopsy following TOOKAD® Soluble- VTP in men with Gleason score 7 (3+4) prostate cancer.

Secondary objectives

The secondary objectives of the study are:

1. To describe the rate of responders, with response defined as the absence of any Gleason pattern 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 pattern 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 occurrence of adverse events of TOOKAD® Soluble VTP treatment in patients with localized prostate cancer
8. To describe the occurrence of severe prostate cancer-related events: cancer extension to T3, metastasis and prostate cancer-related death

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

Endpoints

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.

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).

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 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
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- 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.

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

Study design

Assessments and study duration

This is a single center, single-arm, open-label, 60-month follow-up phase IIb clinical trial with assessments at 3, 12, 24, 36, 48 and 60 months.

Planned sample size

For an assumed true response rate of 83.6%, we can discount a response rate of 70% at a one-sided alpha of 10%, with a power of 80% if we have a sample size of 44 patients.

Interim analyses

No interim analysis is planned during the study. However, this does not preclude an analysis of the primary endpoint after all data on this endpoint are available, that is after the last patients have completed the Month 12 visit. No further analysis of the primary endpoint will be done after results of this analysis have been published.

Analysis populations

Safety population (Safety)

The safety population includes all who received any amount of TOOKAD® Soluble or initiated any study treatment related procedure (including initiation of pre-procedure anesthesia). The safety population will be used for all safety endpoints.

Efficacy population

The efficacy population will include patients who complied with the protocol for inclusion criteria and exclusion and follow-up 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, had no major protocol deviations and provided data at the 12 month biopsy. A "major" protocol deviation is defined as one which, in the opinion of the PI, could importantly influence the result of the 12 months biopsy and which is adjudicated before the 12-month biopsy.

Statistical Considerations and analysis

Derived variables

Total number of positive cores

The total number of positive cores observed during follow-up is calculated by adding the maximum number of positive cores observed in each of the right and left lobes.

Time to stage progression

The time to progression will be calculated from the date of the procedure to the date of stage progression defined as the earliest date of onset of one of the following events, whichever occurs the earliest:

- Extracapsular extension confirmedwithtissue sampling

- Seminal vesical invasion confirmedwithtissue sampling
- Metastasis based on tissue confirmation with biopsy or post-mortem evaluation
- Cancer-related death will be assessed based on tissue confirmation with biopsy or post-mortem evaluation.

Subjects with no documented stage progression will be censored at the date of the last available on study disease assessment.

Time to additional radical therapy (Days)
The time to additional radical therapy will be calculated from the date of treatment to the date of initiation of the first radical therapy. If a subject did not receive any additional radical therapy during the study then the time to additional radical therapy for this subject will be censored at the study termination date.

Time since diagnosis (Months)
The time since diagnosis will be calculated from the date of diagnosis to the date of treatment.

Age
Age (years) = (date of informed consent – date of birth)/365.25 rounded to the lowest integer.

Body Mass Index (BMI)
BMI (kg/m²) = Weight (kg) / (Height (m) * Height (m)).

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 fibres (in cm) per cubic centimeter of the targeted zone. It is calculated as:
TI = (Total length of illumination tip of the fibre)/treatment volume
Where:

- The Total length of illumination tip of the fibre is the sum of the length of each illumination tip of the fibres used during the procedure for the treated lobe or quadrant. The volume of the targeted zone is calculated precisely by the prostate MRI conducted pre-treatment.
- An LDI equal or superior to 1.0 should be achieved for each zone to be treated.

Baseline value
Baseline value will be defined as the last reported value until the date of treatment.
For those patients with two biopsies at baseline the following definitions of baseline values will be applied:
Baseline number of positive cores
Maximum number of positive cores in the left lobe across both biopsies + maximum number of positive cores in the right lobe across both biopsies.
Baseline maximum cancer core length
Maximum cancer core length in the left lobe across both biopsies + maximum cancer core length in the right lobe across both biopsies.
Baseline total cancer core length
Maximum total cancer core length in the left lobe across both biopsies + maximum total cancer core length in the right lobe across both biopsies.

Handling of missing data and/or invalid data and outliers

IIEF questionnaire

Subscale scores with at least 1 but not more than 50% missing items will be imputed using the formula: S = s × T ÷ t where s is the observed score, S is the imputed score, T is the maximum total score for the subscale and t is the maximum score possible from the completed questions. Missing subscale scores will be imputed using a multiple imputation method (Markov Chain Monte Carlo method).

IPSS questionnaire

Scores with at least 1 but not more than 50% missing items will be imputed using the formula: S = s × T ÷ t where s is the observed score, S is the imputed score, T is the maximum total score for the IPSS and t is the maximum score possible from the completed questions. Missing total scores will be imputed using a multiple imputation method (Markov Chain Monte Carlo method).
Other missing data, including biopsy data, will not be replaced.

A subject with missing Month 12 biopsy will be counted as failure for the primary analysis.

Statistical plan and methods

All analysis will be carried out using contemporary versions of Stata or R.
The data collected in this study will be listed for each subject and summarized as appropriate for each treatment group as described below.
Continuous variables will be described using: number of available observations, median, first quartile (Q1), third quartile (Q3) using three significant figures.
Qualitative variables will be summarized by number of observations and percentages (%). Percentages will be rounded to two significant figures and will be based on available observations, unless otherwise specified.

Background characteristics

Subject disposition

The overall number of screen failures will be presented.
The number of subjects consented, who completed the study, who discontinued early and the reasons for early terminations will be summarized by treatment group.
The number of subjects recieving retreatment at 3 months will be presented.

Demographic and baseline characteristics

Demographic characteristics such as age, gender, ethnic origin, height, weight and BMI will be summarized.
Specific baseline disease characteristics such as time since diagnosis, TNM staging, PSA, prostate volume, type of disease (unilateral/bilateral), total number of positive cores will be summarized.

Treatment modalities

The number of fibres used, the energy applied and the light density index will be summarized for the VTP treatment group using standard descriptive statistics.

Efficacy analysis

All analyses will include the “efficacy population” as described above with s secondary analysis including patients undergoing retreatment at 3 months.

Primary efficacy analysis

The proportion of patients with no pattern 4 or 5 found in the 12 month biopsy will be reported along with a one-sided 90% confidence interval. Patients who have pattern 4 or 5 found before 12 months and who receive radical therapy will be treated as treatment failures. The treatment will be considered a success if the lower bound, rounded to 0.01, is 70% or higher. For a sample size of 44, this means that treatment will be declared a success if 35 or more patients respond.

Secondary efficacy analysis

Biopsy results

Biopsy results at each follow-up (3, 12, 24, 36, 48 and 60) for each definition of positive biopsy will be given as cumulative frequency, along with 95% C.I., with radical therapy as a competing risk. The alternative definitions of positive biopsy are:

1. Presence of any pattern 4 or 5 disease (primary endpoint)
2. Presence of cancer of any grade
3. Presence of any pattern 4 or 5 disease in the treated lobe
4. Presence of cancer of any grade in the treated lobe

Analyses will be repeated with radical treatment counted as an event. As retreatment at 3 months is allowed, 3 month results will be treated as a binary endpoint with 95% C.I. presented in a table.

Initiation of additional therapy

Additional prostate cancer treatment is defined as any treatment for prostate cancer other than TOOKAD® Soluble-VTP, including surgery, radiotherapy (external beam, brachytherapy, focused), high intensity focused ultrasound, cryotherapy, hormonal therapy for cancer, chemotherapy for cancer.
The time to initiation of therapy will be analyzed using Kaplan-Meier estimates, presented as a survival curve with corresponding 95% confidence intervals. Subjects who did not initiate any therapy will be censored at the time of study termination. The corresponding Kaplan-Meier curve will also be presented. As a sensitivity analysis, this analysis will be repeated excluding ablative therapies and hormonal therapy, that is, an analysis of time to radical therapy (surgery, radiotherapy). Tables and figures will be provided as appropriate.

Safety analysis

All safety analyses will be based on the safety population. A secondary analysis will include only those patients receiving retreatment at 3 months. Results will be tabulated.

Adverse events

Distinctions will be made between the adverse events not related to the study treatment, related to the study treatment or related to the technical procedure of the VTP. Frequencies of AEs will be tabulated by treatment arm and the proportions of patients exhibiting each AE will be displayed. The adverse events will be classified according to MedDRA version 23.1 or higher.
The treatment-emergent adverse events (adverse events starting after the treatment) will be summarized by System Organ Class (SOC) and preferred term. In addition, the adverse events will be classified according to the NCI Common Terminology Criteria for Adverse Events which is a safety end point of the study. Tabulations will also be made for the System Organ Class, intensity, relationship, seriousness, and attribution corresponding to each AE. Separate tabulations will be made for SAEs.

IPSS (International Prostate Symptom Score) questionnaire

The IPSS score will be calculated as the sum of answers to questions 1 to 7. Prostate related quality of life will be derived from question 8. Descriptive summaries of change from baseline scores at each assessment visit will be provided for both Observed Cases and a multiple imputation method approaches.

IIEF (International Index of Erectile Function) questionnaire

All items will be scored in 5 domains as follows:

- Erectile Function: sum of items 1, 2, 3, 4, 5 and 15 (score range: 1-30).
- Orgasmic Function: sum of items 9 and 10 (score range: 0-10).
- Sexual Desire: sum of items 11 and 12 (score range: 2-10).
- Intercourse Satisfaction: sum of items 6, 7 and 8 (score range: 0-15).
- Overall Satisfaction: sum of items 13 and 14 (score range: 2-10).

Descriptive summaries of the change from baseline will be provided for both Observed Cases and a multiple imputation method approaches.
In addition the erectile function score will be dichotomized as 22 or above vs. 21 and below and the proportion of cases with new onset erectile dysfunction at each timepoint (i.e. baseline score ≥22 but follow-up score < 22) will be reported. For a secondary analysis, new onset erectile dysfunction will be described as baseline score ≥22, follow-up score <22 and change from baseline of more than 2 points.

Clinical laboratory evaluation

Laboratory values will be individually listed by patient number. Values outside the laboratory reference ranges will be flagged on these individual data tables. The investigator will assess whether the values outside of the reference ranges are clinically significant or clinically non-significant. Lab abnormalities will be graded using the NCI Common Terminology Criteria for Adverse Events.
For those parameters that can be graded according to the NCI Common Terminology Criteria for Adverse Events, summaries of shift from baseline in toxicity grade to each post-baseline visit will be provided.
For those parameters that cannot be graded, frequencies of patients' transitions between normal and abnormal not clinically significant (NCS) and abnormal clinically significant (CS) categories will be tabulated.

Vital signs

Descriptive statistics for raw and change from baseline at each planned assessment will be provided by treatment group for oral temperature, blood pressure and pulse rate using both the continuous measure and the proportion of patients outside the reference range (>38°C, >120/80 and 60 – 100, respectively) and will be presented in a table.

Physical exam

All physical examination data and abnormalities will be listed.

Changes from the planned analysis in study protocol

References

The documents used to prepare this SAP include:

- MSKCC IRB protocol 17-070 A(2)

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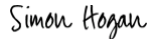
Simon Hogan s.hogan@stebabiotech.com EU Medical Affairs Lead STEBA Biotech Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: D37CB9E9-BA4D-47E7-A839-85580847AB82 Using IP Address: 151.226.30.116 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/4/2021 5:30:49 PM Viewed: 1/4/2021 5:31:41 PM Signed: 1/4/2021 5:32:05 PM
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