A European randomised Phase 3 study to assess the efficacy and safety of TOOKAD® Soluble for localised prostate cancer compared to Active Surveillance

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Primary Objective:To assess the impact of TOOKAD® Soluble VTP on the rate of absence of definite cancer using patients onactive surveillance as a comparison (co-primary objective A).To determine the difference in risk of treatment failure associated...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON41452

Source
ToetsingOnline

Brief title
Treatment of prostate cancer with WST11

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Steba Biotech SA

Source(s) of monetary or material Support: Steba Biotech SA

Intervention

Keyword: cancer, photodynamic therapy, prostate

Outcome measures

Primary outcome

Co-primary endpoint 'A'

Absence of any histological result definitely positive for cancer.

Co-primary endpoint 'B'

Failure of treatment due to progression of cancer from low to moderate or higher risk over the 24 month followup. Moderate or higher risk is defined as the observation of:

• More than 3 cores positive for cancer when considering all histological examination available during follow-up of study;

• or any Gleason primary or secondary pattern 4 or more;

• or at least one cancer core length greater than 5 mm;

• or PSA>10ng/mL in 3 consecutive measures;

• or any T3 prostate cancer;

• or any metastasis;

• or any prostate cancer related death.

Histological changes are assessed at 12 and 24 months using from 10 to 24 cores TRUS biopsies, with the same number and distribution of core samples per zone used for the initial biopsy at study entry or 1 core per 2 cc of tissue in case of significant prostate shrinkage, or any other

pathology result obtained during the study planned or not. The follow-up is done up to loss to follow-up, early study termination or 24 months after randomisation, whatever the treatment events occurring (drop-out, radical treatment). A panel blinded to the exposure status reviews the histological reports of all patients, whether reported positive or negative for cancer, and all the PSA data.

Secondary outcome

• Notification of initiation of radical therapy

• Total number of cores positive for cancer

• Patients* reported outcome measures (PROMs) impairment: urinary symptoms, erectile functions

• Adverse event reporting

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

Quality of life will also be described.

Study description

Background summary

In the year 2006, 300 000 men were diagnosed with prostate cancer in the European community, where prostate cancer was the most commonly diagnosed cancer in men, and the third commonest cause of cancer related death. Prostate cancer is the second most common cause of cancer related death in the US, where it accounts for 3% of all male deaths and is currently the leading type of cancer in men, representing one third of incident cancer cases. In 2009, an estimated 192 000 new cases were diagnosed and 27 000 men died of prostate cancer in the US. Among patients diagnosed with prostate cancer, 46%- are reported as being at low risk, 30% at moderate risk and 24%% at high risk according to the D*Amico classification.3,4 The widespread use of PSA screening

in the clinical practice, including primary care, led to an increased proportion of disease being diagnosed at early, low risk stages, resulting in a very high societal burden.

Conventional radical therapies comprise radical surgery and radiation therapies (brachytherapy, external beam radiation). Cryotherapy is also offered in certain centres, as well as high intensity focused ultrasound (HIFU). The efficiency of radical therapy in low risk prostate cancer is not documented. Evidence of the efficacy of radical treatments may be inferred from randomised controlled trials assessing the role of PSA screening (where men with prostate cancer were most commonly treated with radical therapies). The US trial has shown no difference in prostate cancer related mortality between PSA screening and the control group over a period of 7 years. This study has been criticised for having a high degree of contamination in the control group (many entered the trial already having had a PSA test). The European Screening trial has shown that screening does reduce the cancer-specific mortality over a period of 10 years. According to the European trial, 1410 men would need to be screened, 48 diagnosed and treated (with radical therapy mainly) for cancer in order so one man*s life could be saved. However, it has been suggested that these studies may have underestimated the baseline risk of mortality. Significant rates of positive margins may be found after either surgery or positive biopsies after radiation therapy.
The main problem with radical therapies is safety. Despite technological refinements in radiation therapy (brachytherapy, intensity modulated radiation therapy -IMRT-, and proton therapy as alternatives to external beam radiation) and surgery (laparoscopic and robotic surgery as alternatives to radical prostatectomies), radical whole-gland therapies cause erectile dysfunction in 30-70%, incontinence (requiring pad usage) in 5-10%, and rectal symptoms (diarrhoea, bleeding, proctitis) in 5-20% of treated patients. This occurs because all radical therapies treat the whole prostate regardless of the cancer volume within the prostate and thus, structures that are in close proximity to the prostate (neurovascular bundles, urinary sphincter, bladder neck and rectum) get damaged.

The currently accepted alternative to radical therapies is active surveillance. This primary management strategy involves 2 to 3 monthly PSA testing, clinical examination, and 1 to 2 yearly repetition of transrectal ultrasound (TRUS) guided biopsies to ensure that were progression was to occur, it would be detected early and curative therapy instituted if appropriate.

Although prostate cancer is one of the rare cancers to benefit from the existence of an easily applicable tool for early diagnosis, i.e. PSA testing, most countries avoid recommending general or systematic screening fearing the consequences of more radical therapies that may follow, notably side effects. This represents a loss of opportunity for patients who are not tested and may benefit from earlier diagnosis (a significant fraction of cancers are diagnosed at actual moderate to high risk, and prostate cancer is still one of the

leading causes of death).

Focal therapy may offer a middle ground between radical therapy and active surveillance, the two available extremes of care. Focal therapy proposes to treat prostate cancer with a similar approach as other solid organ malignancies. That is, treatment is directed to the area of cancer and nearby normal tissue in order to preserve tissue and, as a consequence, organ function. By avoiding damage to the whole prostate, damage to the nerves, muscle, urinary sphincter, bladder and rectum can be avoided.

Study objective

Primary Objective:
To assess the impact of TOOKAD® Soluble VTP on the rate of absence of definite cancer using patients on
active surveillance as a comparison (co-primary objective A).

To determine the difference in risk of treatment failure associated with observed histological progression of
disease in men with low risk prostate cancer who undergo TOOKAD® Soluble VTP compared to men on active
surveillance (co-primary objective B).

Secondary endpoints:
To determine the differences between men who undergo TOOKAD® Soluble VTP and men on active
surveillance with regard to:
• the rate of additional prostate cancer radical therapy
• the total cancer burden in the prostate
• the rate of adverse events
• the rate of incontinence, erectile dysfunction, urinary symptoms
• the rate of severe prostate cancer related events: cancer extension to T3, metastasis and prostate cancer related
death.
The overall quality of life will be recorded for potential utility and descriptive studies.

Study design

The study is designed as a phase III randomised controlled open label trial.
Men with low risk prostate cancer will be randomised to active surveillance or TOOKAD® Soluble VTP. Men in the VTP arm will then undergo multiparametric MRI for morphometric description of prostate followed by transrectal ultrasound-guided biopsy (from 10 to 24 cores), to allow accurate treatment planning prior to the VTP procedure. Each group will be followed-up with PSA

testing, clinical evaluation and patient reported questionnaires on a 3 monthly basis. In addition, each group will have multiparametric MRI followed by transrectal ultrasound-guided prostate biopsy at 12 and 24 months after randomisation to active surveillance or TOOKAD® Soluble VTP.

Intervention

In order to activate the treatment, patients must undergo Vascular Targeted Photodynamic therapy (VTP). 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. Transrectal ultrasound is used to view the prostate and the implant catheters. A transperineal template is used to guide the placement of the flexible hollow implant catheters into the prostate. These have a metal trocar 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 implant catheter the metal trocar is removed and replaced with a cylindrically diffusing optical fibre.

WST11 will be delivered in glass vials which must be reconstituted in a 5% glucose solution for injection prior to being injected. This will be injected intravenously during the VTP procedure. The dosing will be 4mg/kg body weight and treatment will consist of one injection.

Study burden and risks

For those patients randomised to VTP:
The risks related to the general anaesthetic are the same as with any such procedure. These may include nausea on waking up, transient soreness in the throat (from the tube used to maintain your breathing) and some loss of concentration for the first few hours after waking up. Serious complications of anaesthesia for this sort of procedure are extremely rare.

There are some other risks related to the drug itself, which are outlined below. You must be aware that both the study drug and the device that is used to activate it (laser) are experimental. Therefore possibility of unknown risks exists in this study as in all other research studies. This procedure may have effects that no one knows about.

For those patients randomised to Active Surveillance:
As the tumour will remain untreated, it can progress in size and aggressiveness. This risk is considered as low and you will be closely followed-up (every three month) to ensure that, should such a progression occur, it would be detected early and curative therapy could be instituted if appropriate.

For all patients:
There is a small risk of infection or bleeding when needles are inserted into the prostate to take a small piece of tissue for examination under the microscope (biopsy).
Some patients find magnetic resonance imaging (MRI) claustrophobic as it is necessary to slide your pelvis into a large machine and the machine can be rather noisy during the imaging. Making it possible to listen to pleasant music during the procedure helps the latter.

The research may involve unforseeable risks to unborn children.

The risk profile attributed to WST11 is favourable compared with alternative therapies.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Low risk prostate cancer diagnosed using one transrectal ultrasound guided biopsy (TRUS) using from 10 to 24 cores, within 12 months of enrolment, and showing the following:;• Gleason 3 + 3 prostate adenocarcinoma as a maximum,;• Two (2) to three (3) cores positive for cancer. Patients with only one positive core can be included provided they have at least 3 mm of cancer core length.;• A maximum cancer core length of 5 mm in any core;;2) Cancer clinical stage up to T2a (pathological or radiological up to T2c disease permitted);;3) Serum prostate specific antigen (PSA) of 10 ng/mL or less;;4) Prostate volume equal or greater than 25 cc and less than 70 cc;;5) Male subjects aged 18 years or older.

Exclusion criteria

1) Unwillingness to accept randomisation to either of the two arms of the study.
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) Life expectancy less than 10 years.
5) Any condition or history of illness or surgery that may pose an additional risk to men undergoing the VTP procedure.
6) Participation in another clinical study or recipient of an investigational product within 1 month of study entry.
7) Subject unable to understand the patient's information document, to give consent or complete study tasks. Subject in custody or in residence in a nursing home or rehabilitation facility.
8) Contra-indication to MRI (e.g., pacemaker, history of allergic reaction to gadolinium), or factors excluding accurate reading of pelvic MRI (e.g., hip prosthesis).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-08-2011
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	Laser Device and Dosimeter
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	TOOKAD® Soluble
Generic name:	Padeliporfin

Ethics review

Approved WMO Date:	08-10-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-02-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-06-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-07-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	08-09-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-10-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-01-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-01-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-05-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-07-2012
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-08-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-12-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-01-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-021900-93-NL
ClinicalTrials.gov	NCT01310894
CCMO	NL33671.060.10