EXPLORATORY CLINICAL TRIAL USING BR55 TARGETED ULTRASOUND CONTRAST AGENT IN THE DETECTION OF PROSTATE CANCER BY MOLECULAR IMAGING OF VEGFR2

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Primary Objective:To assess the ability of BR55 to identify area(s) of VEGFR2 expression in human prostate by ultrasound molecular imaging on the basis of a visual score in comparison with histopathology analysis (location based on expression of...

Ethical review	Approved WMO
Status	Pending
Health condition type	Reproductive and genitourinary neoplasms gender unspecified NEC
Study type	Observational invasive

Summary

ID

NL-OMON34701

Source
ToetsingOnline

Brief title
BR55 in prostate cancer: an exploratory clinical trial

Condition

- Reproductive and genitourinary neoplasms gender unspecified NEC
- Prostatic disorders (excl infections and inflammations)

Synonym
focal prostate lesion, prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Bracco Imaging S.p.A
Source(s) of monetary or material Support: Bracco Imaging SpA

Intervention

Keyword: BR55, Prostate cancer, Ultrasound molecular imaging, VEGFR2

Outcome measures

Primary outcome

A - Contrast enhancement scores:

0. No enhancement: No contrast enhancement is detected within the target lesion

1. Slight enhancement: Presence of minimal BR55 contrast enhancement in the

target lesion

2. Moderate enhancement: Presence of moderate BR55 contrast enhancement in the

target lesion

3. Strong enhancement: Presence of strong BR55 contrast enhancement in the

target lesion.

B - Histopathology and Immunohistochemistry assessments

Secondary outcome

Same as primary

Study description

Background summary

Neo-angiogenesis is the process by which new blood capillaries are formed from existing blood vessels. In the case of cancer lesion as early as they can reach a size of 1.2 mm, the process of neo-angiogenesis is initiated and maintained

by growth factors, cytokines and a range of other chemical mediators. In particular, Vascular Endothelial Growth Factor (VEGF) is an important mediator of angiogenesis in prostate cancer and its corresponding receptor VEGFR (type 1 or 2) is overexpressed in prostate cancer compared with nonmalignant prostate tissue. Research has also shown that VEGF overexpression is associated with poor outcomes in prostate cancer.
Preclinical studies support a high efficacy of BR55 agent for detecting VEGFR2 receptor.
Although animal experiments showed promising results, the risk of clinical failure remains high for ultrasound targeted agents. The leading cause of failure tends to be lack of efficacy, due in part to the lack of predictive animal models and absence of pre-existing results in humans.
Therefore, before embarking upon a formal development program, it is absolutely necessary to conduct an exploratory clinical trial using BR55 and assess if this targeted agent is able to selectively enhance the echogenic signal in prostate cancer lesions compared to surrounding normal parenchyma and the eventual association of such specific enhancement with the overexpression of VEGFR2 in the tumoral tissue compared to the normal parenchyma.

Study objective

Primary Objective:
To assess the ability of BR55 to identify area(s) of VEGFR2 expression in human prostate by ultrasound molecular imaging on the basis of a visual score in comparison with histopathology analysis (location based on expression of VEGFR2 in tissue specimens determined by immuno-histochemistry, IHC).

Secondary Objective:
To evaluate the specificity of BR55 targeting for prostate cancer relative to normal prostate gland on the basis of a visual score in comparison with routine histopathology analysis and IHC assessment of VEGFR2 expression in tissue specimens.

Study design

This is an exploratory phase, single centre, open label, prospective study to assess the ability of the lipopeptide BRU2248 as an active ingredient to bind with VEGFR2. The new ultrasound targeted contrast agent carrying BRU2248, code name BR55, will specifically enhance
ultrasound signals from malignant tissues in the prostate on the basis of ultrasound detection of over-expression of VEGFR2 in those tissues in comparison to the surrounding normal parenchyma.
The Investigator is requested to enrol 12 patients presenting with at least one focal prostate cancer lesion as established by previous biopsies and already scheduled for prostatectomy. This lesion will be further referred as *target prostate lesion* throughout this protocol.

All the enrolled patients with focal prostate cancer lesion will be submitted to the Transrectal Ultrasound diagnostic imaging procedure incluing Contrast Enhanced Ultrasound (CEUS) with BR55 agent.
The study will be conducted in two steps:
1) The dose(s) of 0.01 mL/kg (dose A) and 0.02 mL/kg (dose B) (in case of no enhancement detected with the dose A) of BR55 will be used for the 1st and 2nd bolus respectively in the first 4 patients. In case of positive contrast enhancement within the prostate, the same
dose(s) will be used for the other 8 patients.
2) In case of no observed binding within targeted prostate lesion by visual assessment in step 1 despite positive IHC results, the injected dose(s) will be increased to: 0.03 mL/kg (dose C) and 0.05 mL/kg (dose D) (in case of no enhancement detected with the dose C) for the 1st and 2nd bolus respectively in the last group of patients to overpass possible low sensitivity of ultrasound methods.
The final diagnosis will be obtained for all patients through the histological examination of the prostate gland following prostatectomy.

Intervention

all enrolled patients will receive the BR55 contrast agent.1) The dose(s) of 0.01 mL/kg (dose A) and 0.02 mL/kg (dose B) (in case of no enhancement detected with the dose A) of BR55 will be used for the 1st and 2nd bolus respectively in the first 4 patients. In case of positive contrast enhancement within the prostate, the same
dose(s) will be used for the other 8 patients.
2) In case of no observed binding within targeted prostate lesion by visual assessment in step 1 despite positive IHC results, the injected dose(s) will be increased to: 0.03 mL/kg (dose C) and 0.05 mL/kg (dose D) (in case of no enhancement detected with the dose C) for the 1st and 2nd bolus respectively in the last group of patients to overpass possible low sensitivity of ultrasound methods.
The final diagnosis will be obtained for all patients through the histological examination of the prostate gland following prostatectomy.

Study burden and risks

BR55 is a new targeted ultrasound contrast agent developed for ultrasound molecular imaging of VEGFR2. This agent is made of perfluorobutane/nitrogen microbubbles and a biospecific lipopeptide BRU2248 inserted in the membrane to target VEGFR2.
The components of BR55 have been selected on the basis of their ability to generate stable bubbles, on safety studies, and good imaging performance.
Extensive preclinical toxicological studies performed on the microbubble contrast agent BR55 did not show particular safety concerns.
In the animal models which were imaged with BR55, higher specific attachment

was observed in the tumour site in comparison with non-targeted bubbles or non tumoral lesions suggesting an accurate detection of cancer lesions at early stage.
In conclusion, the data from the preclinical studies with BR55 support a protocol for an exploratory Phase in patients as a proof of concept of efficacy in humans, with doses starting at a dose level of 0.01 mL/kg.
The planned study is an exploratory trial in which the dose of active agent to be studied is lower than 100 *g.
There is no expected risk for the patient.

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

* Male patient, age * 40 years old

* Has a histology proven focal prostate cancer lesion
* The patient is already scheduled for prostatectomy not earlier than 3 days and at the latest 15 days after BR55 administration
* Provides written Informed Consent and is willing to comply with protocol requirements

Exclusion criteria

* Has a body weight greater than 95 kg (this weight limitation is required in order to maintain the active component of the drug under 100*g) according to the indication of the EMEA guideline M3 for this type of study
* Has documented acute prostatitis or urinary tract infections
* With history of any clinically unstable cardiac condition including class III/IV cardiac failure or right-to-left shunts
* Has had severe cardiac rhythm disorders within the last 7 days
* Has severe pulmonary hypertension (pulmonary artery pressure >90 mmHg) or uncontrolled systemic hypertension or respiratory distress syndrome
* Has received a prostate biopsy procedure within 30 days before admission into this study
* Has any medical condition or other circumstances which would significantly decrease the chances of obtaining reliable data, achieving study objectives, or completing the study.
* Is determined by the Investigator that the patient is clinically unsuitable for the study.
* Is incapable of understanding the language in which the information for the patient is given
* Participation in a concurrent clinical trial or in another trial with an investigational compound within the past 30 days;

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2010
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable
Generic name:	not applicable

Ethics review

Approved WMO Date:	26-03-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2009-016927-71-NL
CCMO	NL31957.018.10