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A study of intravesical TMX-101 in subjects with Non-Muscle-Invasive Bladder Cancer

Submission date
10/07/2013

Recruitment status
No longer recruiting

Registration date
21/08/2013

Overall study status
Completed

Last Edited
21/08/2013

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
TMX-101 is a new experimental medicine that contains the active molecule imiquimod. TMX-101 is a solution of imiquimod specifically designed for use in the bladder. Imiquimod is the active substance in Aldara®, medication which is already marketed as a cream in many countries in the world. Aldara® is approved for the treatment of various skin disorders including skin cancer (basal cell carcinoma). Imiquimod works by stimulating the immune system, which causes local inflammation and attacks the cancer cells. It is thought that Imiquimod, given as a bladder instillation, stimulates the immune system of the bladder to attack bladder cancer cells present on the surface.
The main purpose of the study is to determine whether TMX-101 is safe and tolerable. The second purpose of the study is to measure TMX-101 in the blood and urine and to evaluate changes in various biological values. The third purpose of this study is to determine the extent to which TMX-101 can eliminate bladder tumours in the short term (after 5 weeks). This will occur by looking at the effect on a marker lesion. This is a small area of the tumour that stays behind during the operation that is performed before the treatment.
Superficial bladder cancer in most cases is a multifocal disorder. This means that tumours develop in different places on the surface of the bladder at the same time. These tumours are called lesions. In this study, keyhole surgery removes all the tumour areas apart from one small area. The reason for leaving the marker lesion is to check whether TMX-101 can eliminate this lesion. International studies in bladder cancer patients have demonstrated that leaving behind a marker lesion for the duration of the study is not harmful.

Who can participate?
Patients diagnosed with low-grade superficial bladder cancer can participate in the study. The staging of the cancer should be defined as Ta or T1.

What does the study involve?
Participation in this study will take at least 11 weeks and 17 weeks at most. Participants will be asked to return for a visit one year after the last instillation. This study involves a total of 10 visits to the hospital.
For those patients who participate in part 1 of the study, the bladder tumour will be totally removed by surgery. They will then receive six bladder TMX-101 instillations once a week for a

total of six weeks. During a bladder instillation, the bladder is filled with a solution of TMX-101 that is held for varying periods of time before being emptied.
For those patients who participate in part 2 of the study, the diagnosed bladder tumour will be removed apart from one small area of the tumour, the marker lesion. They will then receive six bladder TMX-101 instillations once a week for a total of six weeks. The effect on the marker lesion will be evaluated after these six instillations. If there is any residual tumour, it will be removed by a second operation.

What are the possible benefits and risks of participating?
It is not yet known whether TMX-101 can treat bladder cancer in humans. You should therefore not assume that the treatment will work for you. You may not personally benefit from participation in this study. The study may provide useful data for the future.
The most important, though rare, risks associated with the operation (transurethral resection) are: bleeding, bladder infection (cystitis), perforation of the bladder wall, blood in the urine, and blockage of the urethra due to blood clots in the bladder.
The most important risks that can occur during the removal of tissue (biopsy) are: pain and discomfort, mild bleeding, tenderness at the site of the biopsy, scar formation at the site of the biopsy and, rarely, infection.
Another risk may be trauma relating to the bladder catheterisation.
The most important risks associated with blood collection are discomfort and bruising of the needling site. Although rare, localized clot formation and infections may occur. Lightheadedness and/or fainting may also happen during or shortly after drawing blood. In very rare cases permanent nerve damage might occur.
There are no risks associated with leaving behind a tumour lesion for the duration of the study; this has been demonstrated in international studies in patients with the same background as patients included in the study.

Where is the study run from?
The study is run at several hospital sites in Germany and The Netherlands.
Four sites in The Netherlands:
Radboud UMC Nijmegen
AMC University of Amsterdam
Canisius Wilhelmina Hospital Nijmegen
ZGT Hengelo
Three sites in Germany:
Klinik und Poliklinik für Urologie, Uroonkologie und Kinderurologie Universitätsklinikum Essen
Praxisklinik Urologie Rhein-Ruhr, Mülheim an der Ruhr
Urologische Klinik und Poliklinik, Universitätsmedizin der Johannes Gutenberg-Universität Mainz

When is the study starting and how long is it expected to run for?
The study started in April 2010 and ran until July 2013.

Who is funding the study?
Telormedix SA, Switzerland.

Who is the main contact?
telormedix@telormedix.com

Contact information

Type(s)

Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2009-014757-33

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
TMX-101-001

Study information

Scientific Title
A phase I dose escalation study of intravesical TMX-101 in subjects with Non-Muscle-Invasive Bladder Cancer

Study objectives
No hypothesis being tested.
The aim of the study:
Part 1: to perform initial safety assessment during this dose escalation part in patients after complete transurethral resection of the tumor.
Part 2: assessment of EBD (effective biological dose) in patients with a marker lesion.
Part 3: follow-up phase to assess safety and disease status.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval obtained by the Commissie Mensgebonden Onderzoek (Central Ethics Committee) at the UMC St Radboud Centraal in Nijmegen, the Netherlands on the 20th of April, 2010.
Reference numbers: CMO dossiernr: 2009/251, ABR nr.: NL29741.091.09

Study design
Multicentre open-label Phase I dose escalation trial

Primary study design

Interventional

Secondary study design
Non randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Screening

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Non-Muscle Invasive Bladder Cancer (NMIBC) / urinary bladder cancer / oncology

Interventions
An open-label Phase I dose escalation trial that will follow a standard escalation design with cohorts of 3 patients per dose level. TMX-101 will be given once a week for 6 weeks.

Two-three weeks before treatment:
The bladder will be mapped by video cystoscopy; cytology, TUR and biopsies will be performed. Histology will be performed to confirm inclusion criteria. Patients eligible for the Effective Biological Dose assessment (EBD) assessment (Part 2) will not undergo a complete TUR and a single marker lesion between 0.5 to 1 cm in diameter will be left in place. Tumour samples and one sample of normal-appearing mucosa from the biopsy will be used for the evaluation of biomarkers in patients entering the Part 2 of the study.

Treatment: Intravesical TMX-101 instillations will be started two-three weeks after the TUR and will be performed every 7 (± 1) days for a total of 6 instillations in 6 weeks.

Four to five weeks after last treatment patients of Part 1 will undergo cytoscopy that includes complete bladder cavity assessment. Cytology will also be performed.

Two-four weeks after the last instillation, the bladder of patients eligible for the EBD assessment (Part 2) will be mapped to evaluate the response of the marker lesion. If the marker lesion is still present it will be resected by TUR. Histology and cytology will be performed.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
intravesical TMX-101 (imiquimod)

Primary outcome measure

1. The number and proportion of subjects experiencing treatment-emergent adverse events (TEAE).
2. The number and proportion of subjects experiencing clinically significant changes in a laboratory parameter and/or vital signs judged to be related to the trial medication.
3. The number and proportion of subjects experiencing at least a Dose-Limiting Toxicity (DLT) over the first 3-week cycle (from Day 0 to 21) at each dose level.
4. The number and proportion of subjects with clinical benefit (defined as CR) based on the tumour evaluation 2-4 weeks after the last instillation (6th instillation).

Safety measures will be assessed at each patient visit throughout the study schedule. Measures are Adverse Events assessments during each study visit; in addition Investigations like physical exam or Vital signs, Blood and Urine parameters assessments at fixed study visits.

Secondary outcome measures
Pharmacokinetics
Plasma and urine PK parameters of TMX-101 and its main metabolites. Measured at several timepoints in selected patients.

Pharmacodynamic
Values and changes over time in pharmacodynamic markers in urine and in blood. Measured at several timepoints in selected patients.

Anti-tumor activity
The anti-tumour activity of TMX-101 will be assessed by summarizing the number and percent of subjects by tumour responses including Complete Response (CR), No Response (NR), Progressive Disease (PD) and Not Evaluable (NE) after 6 weeks of treatment for Part 2 only.

Pharmakokinetic (PK) and Pharmacodynamic (PD) assessments by blood analysis are being performed in defined patients at all visits until end of individual treatment period.
Urine assessments on PK and PD are being assessed from each patient at all visits until end of treatment period.
The anti-tumor activity will be assessed by TUR, cystoscopy and Urine cytology occurring during screening visit. Cystoscopy and Cytology will be repeated at the post-treatment activity assessment visit and at the 1-year Follow-up visit. If cystoscopy reveals new tumors, a TUR will be planned and histology performed.

Overall study start date
20/04/2010

Completion date
31/07/2013

Eligibility

Key inclusion criteria
The study population will consist of patients with non-muscle invasive bladder cancer (NMIBC) who have undergone Transurethral resection (TUR). A complete TUR will be performed in patients entering the first part of the study, while in patients entering the second part of the study a marker lesion will be left for assessment after the TUR procedure.

All patients
1. Age ≥ 18 years.
2. Performance status: ECOG 0-1.
3. Subjects who have read and understood the informed consent form and are willing and able to give informed consent. Subjects who fully understand the requirements of the trial and are willing to comply with all trial visits and assessments.
4. Women of childbearing potential must have a negative blood pregnancy test at the screening visit. For the purposes of this trial, women of childbearing potential is defined as: All female subjects after puberty unless they are post-menopausal for at least two years, are surgically sterile or are sexually inactive.
5. Female subjects of childbearing potential and male subjects with female partners of childbearing potential must be willing to avoid pregnancy by using an adequate method of contraception for 2 weeks prior to, during and four weeks after the last dose trial medication. Adequate contraception is defined as follows: two barrier methods, or one barrier method with a spermicide or intrauterine device.

Patients to enter the first part of the study:
1. Histologically confirmed diagnosis of urothelial carcinoma of the urinary bladder stage Ta with low and high histological grade or T1 with low histological grade.
2. Complete removal of tumours through TUR procedure.

Patients to enter the second part of the study:
1. Histologically confirmed diagnosis of urothelial carcinoma of the urinary bladder stage Ta or T1 with low histological grade.
2. Prior to TUR, multiple tumours but not more than seven.
3. One marker lesion left for assessment after TUR procedure, between 0.5 to 1.0 cm in diameter, documented with video or photo.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
30

Key exclusion criteria
Patients in the first part of the study:
1. Current urinary tract T1 high grade tumour, previous or current history of carcinoma in situ, muscle invasive disease (T2 or higher).
2. Current high grade urinary cytology in subjects with T1 tumour.

Patients in the second part of the study:
1. Current urinary tract Ta high grade tumour, previous or current history of T1 high grade

tumour, carcinoma in situ, muscle invasive disease (T2 or higher).
2. Current high grade urinary cytology
3. Subjects who require immediate complete TUR, as judged by the investigator.

All Patients
1. Any prior intravesical BCG or any other immunotherapy within the last 24 months.
2. Previous intravesical treatment with chemotherapy agents within 6 months of entry into the study.
3. Subjects who cannot hold instillation for at least one hour.
4. Subjects who cannot tolerate intravesical administration or intravesical surgical manipulation.
5. Current or prior pelvic external beam radiation or pelvic brachytherapy.
6. Existing urinary tract infections or recurrent severe bacterial cystitis.
7. History of disease of the upper urinary tracts (e.g. vesico-urethral reflux, indwelling urinary stent, UT stones).
8. Bone marrow impairment as evidenced by Haemoglobin < 9.0 g/dL, ANC 1.5 x 109/L, platelets < 120 x 109/L
9. Renal impairment as evidenced by serum creatinine > 1.5 x ULN, and/or calculated creatinine clearance < 60 mL/min.
10. Liver function abnormality as defined by total bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN.
11. Bleeding disorders as evidenced by INR > 1.5 x ULN.
12. Immunosuppressed patients or patients receiving immunosuppressive therapy or who are otherwise immunocompromised.
13. Known HIV positivity, active hepatitis C, or active hepatitis B.
14. Any other active malignancy within 5 years except study indication, basal or squamous cell skin cancers and cured prostate cancer (PSA below 0.2 ng/mL).
15. Clinically significant active infections within 4 weeks before initial treatment administration.
16. Any medical or psychiatric condition which, in the opinion of the investigator, might impair the subjects well being or preclude him from adhering to the protocol or completing the trial as per protocol.
17. Suspected hypersensitivity to imidazoquinoline compounds, poloxamer 407, hydroxy propyl betacyclodextrin, lactic acid.
18. Women who are pregnant or breast feeding.
19. Participation in any other protocol involving administration of an investigational agent within 3 months prior to entering this study.

Date of first enrolment
20/04/2010

Date of final enrolment
31/07/2013

Locations

Countries of recruitment
Germany

Netherlands

Study participating centre

Radboud UMC Nijmegen
Nijmegen
Netherlands
6525 GA

Sponsor information

Organisation
Telormedix SA (Switzerland)

Sponsor details
Via della Posta 10
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Sponsor type
Industry

Funder(s)

Funder type
Industry

Funder Name
Telormedix SA (Switzerland)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration