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

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The primary objectives are the following:- To assess the safety profile and determine the Optimal Biological Dose (OBD) or Maximum Tolerated Dose (MTD), whichever occurs first, of intravesically administered TMX-101. The secondary objectives are the...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Miscellaneous and site unspecified neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON35119

**Source**
ToetsingOnline

**Brief title**
Dose escalation study of intravesical TMX-101

### Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Bladder and bladder neck disorders (excl calculi)

**Synonym**
Non-Muscle-Invasive Bladder cancer

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Telormedix SA

**Source(s) of monetary or material Support:** Telormedix SA

## Intervention

**Keyword:** Bladder Cancer, Dose escalation, Intravesical instillation, TMX-101

## Outcome measures

### Primary outcome

The primary study parameter is regarding Safety:

During this study, patients will be treated in cohorts of three per dose level until the OBD or MTD is reached, whichever occurs first. The number of patients will increase to six in those cohorts where one out of three patients develops Dose Limited Toxicity (DLT). The safety of the OBD and/or the MTD will be confirmed in at least 6 patients who have received two cycles of TMX-101 therapy.

To ensure safety, each dose level will start with one patient receiving a cycle of TMX-101. The other two patients from the same cohort will start the therapy not less than one week later as long as no serious toxicity is observed in the first patient after the first instillation. If none of the three patients develops DLT, the dose will be escalated. If two or more patients experience DLT, further dosing at that dose level will stop and the dose level immediately below will be considered to be the MTD. Should only one out of three patients at the same dose level experience DLT, the number of patients treated at this dose level will be expanded to six. Provided none of the additional three patients experiences DLT, the dose will be escalated further; otherwise the escalation will stop and the dose immediately below will be deemed to be the

MTD.

- DLT is defined as any of the following toxicities occurred during the first cycle at any dose level which the investigator and/or the sponsor judge to be related to the trial medication.

o Any grade 3 or higher toxicity.

o Any treatment delay >= 21 days due to drug-related adverse events.

- The OBD is defined as Complete Response (CR) (total disappearance of a marker lesion and the absence of new tumours at other sites), as observed in at least three patients. As these patients can be from the different dose levels, the OBD will be considered to be at the highest dose level at which these activities are observed.

- The MTD is defined as the highest dose level at which less than 33% of patients experience DLT (assessed by CTCAE version 4.02) during the first cycle of therapy.

There will be no within-patient dose escalation.

It is planned to have more than one centre involved during the escalation phase. Escalation to a further dose level will occur only after a comprehensive analysis of safety data of each cohort by all investigators and the sponsor during a planned teleconference.

During the escalation phase, patients will visit the centre every week for a clinical examination and adverse events (AEs) and laboratory screens will be assessed at each visit.

Subjects will be monitored carefully for the development of Adverse Events (AE). AEs will be evaluated according to CTCAE, version 4.02.

A 6-hour pharmacokinetic profile of TMX-101 will be assessed in all patients during the dose escalation phase.

In patients eligible for the OBD assessment, the bladder will be mapped to assess the marker lesion 2-4 weeks after the end of the treatment (total of 6 instillations) and, if the marker lesion is still present, it will be resected by TUR.

Tumour measurements will be made by an endoscopic evaluation (cystoscopy) that includes complete bladder cavity assessment.

**Secondary outcome**

(a) Safety

- The number and proportion of subjects experiencing treatment-emergent adverse events (TEAE).
- 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.

(b) Pharmacokinetics

- Plasma and urine PK parameters of TMX-101 and its main metabolites.

(c) Pharmacodynamic

- Values and changes over time in PD markers in urine, blood, and in bladder/tumour tissue samples

(d) To describe the relationship between tumour characteristics (e.g. tumour

immunohistochemistry) and biological activity.

(e) To assess the disease recurrence and progression to muscle invasive disease

within 1 year.

# Study description

**Background summary**

Imiquimod, originally discovered as an *interferon-inducing* molecule, is the active ingredient of Aldara* a cream approved and marketed since 1996 for the topical treatment of genital warts (induced by human papilloma virus, HPV), basal cell carcinoma and actinic keratosis. Imiquimod is a member of the imidazoquinoline family. The imidazoquinolines are small-molecule immune response modulators that are agonists for TLRs 7 and/or TLRs 8. Activation of these TLRs, which are found primarily on cells of the innate immune system results in dendritic cell maturation, induction of multiple cytokines including interferon-alpha (IFN-α), and in enhanced antigen presentation. These immune-stimulating effects are considered to mediate the antiviral and anti-tumour activities observed with these compounds, including effects on both innate and acquired immunity. In addition, imiquimod exerts a direct pro-apoptotic effect on tumour cells resulting in direct antitumor effects. Treatment of skin lesions with imiquimod 5% cream in phase III randomized placebo-controlled studies resulted in histological clearance rates between 79% and 82%. Direct effects of imiquimod have also been reported by groups working on melanoma, non-melanoma skin cancers and precancerous conditions.

Telormedix has developed TMX-101 as a new formulation of imiquimod for intravesical delivery. TMX-101 has been tested as intravesical instillation in several animal models and has been demonstrated to induce a strong immunological activation limited to the bladder. Its systemic absorption measured in various species is <10% of the intravesical dose. Based on existing preclinical and clinical evidence, it is expected that TMX-101 will exert an immunological activation and will show activity against bladder cancer lesions.

This trial will determine the safety and tolerability of escalating doses of intravesical TMX-101 in patients with NMIBC. In addition, it will provide preliminary evidence of activity on a *marker lesion* and thereby indicate whether TMX-101 may potentially offer a valid alternative for the treatment of patients with bladder cancer.

The information obtained from this trial will be essential for the future clinical development of TMX-101 in bladder cancer.

**Study objective**

The primary objectives are the following:
- To assess the safety profile and determine the Optimal Biological Dose (OBD) or Maximum Tolerated Dose (MTD), whichever occurs first, of intravesically administered TMX-101.

The secondary objectives are the following:
- To assess the pharmacokinetics of TMX-101 and its main metabolites in blood and urine.
- To assess biological activity of TMX-101 and pharmacodynamic markers in urine, in blood and in pre/post dosing tumour biopsies.
- To assess the anti-tumour activity of TMX-101 on a marker lesion after 2 cycles (6 intravesical administrations) in a selected group of patients.
- To describe the relations between tumour characteristics (e.g. tumour immunohistochemistry) and biological activity.
- To assess the disease recurrence and progression to muscle invasive disease within 1 year.

**Study design**

This is an open-label Phase I dose escalation trial that will follow a standard escalation design with cohorts of three patients per dose level. TMX-101 will be given in cycles of once a week for three weeks.
The study will consist of three parts. Part 1: initial safety assessment in patients with complete TUR, Part 2: assessment of OBD in patients with a marker lesion and Part 3: follow-up phase.
During Part 1 the doses will be escalated by doubling (100% increments). In Part 2 doses will be escalated by reduced increments of approximately 50%. If significant toxicity is observed the escalation will continue at decreasing rates (Fibonacci - like scheme) from when the first sign of significant toxicity is observed.
During Part 1 the safety of one cycle of TMX-101 will be tested in patients with non-muscle-invasive bladder cancer who have undergone a complete transurethral resection (TUR). These patients will receive a second cycle of TMX-101 therapy if no toxicity or disease progression is observed. Safety data of all subjects that have completed the first cycle of a dosing cohort will be reviewed to determine the next dose level.
During Part 2 the OBD and its safety will be determined in a two-cycle therapy in patients who have one marker lesion remaining after TUR, starting with the highest tested dose level that will have been confirmed to be safe in the patients in Part 1.
During Part 3 all patients (enrolled in Part 1 and Part 2) will be followed to

assess if they experience a recurrence or progression within the first year.
During this study patients will be treated in cohorts of three per dose level until the Optimal Biological Dose (OBD) or Maximum Tolerated Dose (MTD) is reached, whichever occurs first. The number of patients will increase to six in those cohorts where one out of three patients develops Dose Limited Toxicity (DLT). The safety of the OBD will be confirmed in at least 6 patients who have received two cycles of TMX-101 therapy.
To ensure safety each dose level will start with one patient receiving a cycle of TMX-101. The other two patients from the same cohort will start the therapy not less than one week later as long as no serious toxicity is observed in the first patient after the first instillation. If none of the three patients develops DLT the dose will be escalated. If two or more patients experience DLT further dosing at that dose level will stop and the dose level immediately below will be considered to be the MTD. Should only one out of three patients at the same dose level experience DLT, the number of patients treated at this dose level will be expanded to six. Provided none of the additional three patients experiences DLT, the dose will be escalated further; otherwise the escalation will stop and the dose immediately below will be deemed to be the MTD. Alternatively dose de-escalation will be considered.
• DLT is defined as any of the following toxicities occurred during the first cycle at any dose level which the investigator and/or the sponsor judge to be related to the trial medication.
o Any grade 3 or higher toxicity.
o Any treatment delay >= 21 days due to drug-related adverse events.
• The OBD is defined as Complete Response (CR) (total disappearance of a marker lesion and the absence of new tumours at other sites), as observed in at least three patients. As these patients can be from the different dose levels, the OBD will be considered to be at the highest dose level at which these activities are observed.
• The MTD is defined as the highest dose level at which less than 33% of patients experience DLT (assessed by CTCAE version 4.02) during the first cycle of therapy.
There will be no within-patient dose escalation.
It is planned to have more than one centre involved during the escalation phase. Escalation to a further dose level will occur only after a comprehensive analysis of safety data of each cohort by all investigators and the sponsor during a planned teleconference.
During the escalation phase the patients will visit the centre every week for a clinical examination and adverse events (AEs) and laboratory screens will be assessed at each visit. Tumour measurements will be made 2-4 weeks after the end of the two cycles.
Tumour measurements will be made by an endoscopic evaluation (cystoscopy) that includes complete bladder cavity assessment.
A 6-hour pharmacokinetic profile of TMX-101 will be assessed in all patients during the dose escalation phase.
Subjects will be monitored carefully for the development of Adverse Events (AE).

In patients eligible for the OBD assessment, the bladder will be mapped to assess the marker lesion 2-4 weeks after the end of the treatment (total of 6 instillations) and, if the marker lesion is still present, it will be resected by TUR.
AEs will be evaluated according to CTCAE, version 4.02.

**Intervention**

Each subject will receive a first cycle of TMX-101 comprising of one dose given once a week for three consecutive weeks. After the end of the first cycle (day 0 to day 21) if no serious toxicity is noted, the subject will receive, without interruption, one more cycle of the TMX-101 therapy at the same dose level for a total of 6 weekly instillations (from day 0 to day 35).

TMX-101 will be administered intravesically by gravity through a Foley Catheter-12 French. The retention time will be 1 hour.
Instillations will be started at earliest 14 days and at the latest 21 days after the TUR.

**Study burden and risks**

There are risks to taking part in any research study and not all of the risks of TMX-101 are known at this time since to date, no subjects with bladder cancer have received TMX-101. One risk is that there may be unwanted side effects. Another risk is that you may obtain a dose of a drug that does not help to treat your disease.

All drugs currently used for treatment of superficial bladder cancer have side effects, which can range from mild and reversible to severe. Local side effects due to the use of TMX-101 might be similar to those reported with other intravesical treatments and might be:
• Painful urination, irritative bladder symtoms and involuntary contraction of the bladder (spasm). These side-effects usually occur within 24 hours after intravesical instillations and they do resolve spontaneously.
• Presence of blood in the urine.
• Urinating more often than usual, an urgent feeling of having to urinate and general discomfort felt in the bladder.
• Urinary tract infection (bacterial cystitis)

The active molecule contained in this investigational product is imiquimod, the active ingredient of Aldara®, a cream on the market since 1997. Many subjects have been treated to date with imiquimod not only applied to the skin as a cream, but also given by injection under the skin and injected into the blood. The following side effects that occur with imiquimod may also occur with TMX-101:
• Flu-like symptoms: fever, chills, fatigue, muscle aches (myalgia).

• Fatigue, weakness.
• Loss of appetite.
• Upset stomach, nausea (feeling sick to your stomach).
• Headache.
• In some individuals that were treated with Aldara® a lowering of blood cells counts was noted. A lowering of blood counts might make you more susceptible to infections, make you bruise more easily or cause fatigue.
• In some individuals treated with Aldara® elevated liver enzymes were observed. Elevated liver enzymes can be a sign of a liver disorder.

Further information can be found in the Aldara® patient information sheet that can be supplied to you by your doctor or medical staff.

In animal studies with TMX-101, effects on the Central Nervous System (such as seizures) were observed at doses largely above the doses used in this study. In the unlikely case of overdose, you will be monitored for any sign and symptoms on the Central Nervous System.

The main, but rare, risks associated with surgery (transurethral resection) are: bleeding, bladder infection (cystitis), perforation of the wall of the bladder, blood in the urine, blockage of the urethra (water pipe) by blood clots in the bladder. Further information about this surgery will be provided by your study doctor.

The main risks associated with biopsies may include: pain and discomfort, minor bleeding, tenderness at the biopsy site, scarring at the biopsy site and rarely infection.
Biopsies are performed under the guidance of an imaging technique. Further information about biopsy will be provided by your study doctor.

Another risk might be some trauma related to bladder catheterisation. This is unlikely to occur, but in such a case TMX-101 will not be administered and there will be a treatment delay of at least 10 days.

The main risk associated with withdrawal of blood (injection under the skin) is discomfort and bruising at the site of puncture.

## 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

(a) Age at least 18 years.
(b) Histologically confirmed diagnosis of urothelial carcinoma of the urinary bladder stage Ta or T1 with low histological grade.
(c) Performance status: ECOG 0-1
(d) 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.
(e) 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*.
(f) 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:
(g) Complete removal of tumours through TUR procedure
Patients to enter the second part of the study:
(h) Prior to TUR multiple tumours but not more than seven.

(i) One marker lesion left for assessment after TUR procedure, between 0.5 to 1.0 cm in diameter, documented with video or photo.

### Exclusion criteria

(a) Previous or current history of urinary tract high grade tumour, carcinoma in situ, muscle invasive disease (stage T2 or higher).
(b) Any prior intravesical BCG or any other immunotherapy within the last 24 months.
(c) Previous intravesical treatment with chemotherapy agents within 6 months of entry into the study.
(d) Subjects who cannot hold instillation for at least one hour.
(e) Subjects who cannot tolerate intravesical administration or intravesical surgical manipulation.
(f) Current or prior pelvic external beam radiation or pelvic brachytherapy.
(g) Existing urinary tract infections or recurrent severe bacterial cystitis.
(h) History of disease of the upper urinary tracts (e.g. vesico-urethral reflux, indwelling urinary stent, UT stones).
(i) High grade urinary cytology.
(j) Bone marrow impairment as evidenced by Haemoglobin < 9.0 g/dL, ANC 1.5 x 109/L, platelets < 120 x 109/L
(k) Renal impairment as evidenced by serum creatinine > 1.5 x ULN, and/or calculated creatinine clearance < 60 mL/min.
(l) Liver function abnormality as defined by total bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN.
(m) Bleeding disorders as evidenced by INR > 1.5 x ULN.
(n) Immunosuppressed patients or patients receiving immunosuppressive therapy or who are otherwise immunocompromised.
(o) Known HIV positivity, active hepatitis C, or active hepatitis B.
(p) Any other active malignancy except study indication and basal or squamous cell skin cancers.
(q) Clinically significant active infections within 4 weeks before initial treatment administration.
(r) Any medical or psychiatric condition which, in the opinion of the investigator, might impair the subject*s well being or preclude him from adhering to the protocol or completing the trial as per protocol.
(s) Suspected hypersensitivity to imidazoquinoline compounds, poloxamer 407, hydroxy propyl betacyclodextrin, lactic acid.
(t) Women who are pregnant or breast feeding.
(u) Participation in any other protocol involving administration of an investigational agent within 3 months prior to entering this study.

## Study design

## Design

**Study type:** Interventional

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 11-06-2010 |
| Enrollment: | 21 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Imiquimod |
| Generic name: | Imidazoquinoline |
| Registration: | Yes - NL outside intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 24-02-2010 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 20-04-2010 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 29-03-2011 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 21-07-2011 |

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|---|---|
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 17-04-2012 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 11-05-2012 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 28-09-2012 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 21-02-2013 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |

# 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 | EUCTR2009-014757-33-NL |
| CCMO | NL29741.091.09 |