Phase 1 Study of Erdafitinib Intravesical Delivery System (TAR-210) in Participants with Non-Muscle-Invasive or Muscle-Invasive Bladder Cancer and Selected FGFR Mutations or Fusions

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primary objectives:* Part 1 (dose escalation): To determine therecommended Phase 2 dose(s) (RP2D[s]) forTAR-210* Part 2 (dose expansion): To determine thesafety of TAR-210 administered at theRP2D(s)for up to 12 monthsSecondary objectives (Parts 1…

Ethical review	Approved WMO
Status	Will not start
Health condition type	Renal and urinary tract neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON53522

Source
ToetsingOnline

Brief title
Ph1 Study of Erdafitinib Intravesical Delivery System for Bladder Cancer

Condition

- Renal and urinary tract neoplasms benign

Synonym
Localized Bladder Cancer, Non-Muscle-Invasive or Muscle-Invasive Bladder Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: The Sponsor of the Study

Intervention

Keyword: Bladder Cancer, Erdafitinib, Intravesical Delivery system, Safety

Outcome measures

Primary outcome

Endpoints:

*Incidence and severity of AEs, including dose-limiting toxicity (DLT)

Secondary outcome

Endpoints: *Plasma and urine concentration-time profiles and PK parameters for

erdafitinib Cohorts 1 and 2: * Recurrence-free survival (RFS) Cohort 3: *

Complete response (CR) rate * Duration of CR Cohort 4: * Pathological complete

response (pCR) rate * pT0 rate * Rate of downstaging to

Study description

Background summary

TAR-210 is a drug delivery system that delivers a drug called erdafitinib directly into the bladder. It is also sometimes referred to as the erdafitinib intravesical delivery system. TAR 210 is a pretzel-shaped tube. It is placed in the bladder with a urinary placement catheter. TAR-210 is designed to release a controlled amount of erdafitinib (an anti-cancer drug). Erdafitinib is an anticancer medication approved by the U.S. Food and Drug Administration, or "FDA," for the treatment of patients with more advanced and metastatic types of bladder cancer with an FGFR gene alteration. Erdafitinib is an FGFR inhibitor, which means it blocks the activity of a protein called fibroblast growth factor receptor (FGFR). Erdafitinib is currently used as an oral medication (pill taken by mouth). Erdafitinib has demonstrated efficacy in participants with locally advanced or metastatic urothelial carcinoma. Oral erdafitinib is not

approved to treat NMIBC or MIBC.

Study objective

primary objectives:
* Part 1 (dose escalation): To determine the recommended Phase 2 dose(s) (RP2D[s]) for TAR-210
* Part 2 (dose expansion): To determine the safety of TAR-210 administered at the RP2D(s)for up to 12 months

Secondary objectives (Parts 1 and 2) :
* To assess the PK
* To assess preliminary clinical activity

Study design

This is an open-label, multicenter, Phase 1 study of the safety, PK, and preliminary efficacy of TAR-210 in adult participants with either NMIBC or MIBC. All participants will be screened for eligible FGFR mutations or fusions.
The study will enroll 4 cohorts of participants.
* Cohort 1: Recurrent, BCG-experienced high-risk papillary NMIBC (high-grade Ta/T1), refusing or ineligible for RC.
* Cohort 2: Recurrent, BCG-experienced high-risk papillary NMIBC (high-grade Ta/T1), scheduled for RC.
* Cohort 3: Recurrent, intermediate-risk NMIBC (Ta and T1) with previous history of only low-grade disease.
* Cohort 4: MIBC scheduled for RC who have refused or are ineligible for cisplatin-based neoadjuvant chemotherapy

The study will comprise 2 parts: Part 1 (dose escalation) and Part 2 (dose expansion). The study will initially enroll participants in Cohorts 1 and 3 in Part 1, dose escalation. Participants in each of the 4 cohorts may be enrolled in Part 2, dose expansion, at a given dose level after that dose level has been determined to be safe in Part 1.

An eligible FGFR alteration must be identified prior to start of study

treatment.

The study comprises molecular eligibility, screening, treatment, and follow-up phases

Intervention

TAR-210 Drug-device combination product Intravesical system.

Study burden and risks

Potential Discomforts, Side Effects, and Risks Associated with TAR-210
Side effects are unwanted symptoms caused by a drug. All drugs can cause side effects. Most side effects will go away after the patient stops treatment, but some may be long lasting. Even if previous studies have shown that the study treatment is normally well tolerated, the patient may still experience side effects.

The possible discomforts, side effects, and risks related to TAR-210 treatment are not known. Possible risks are based on testing of TAR-210 in animals and the risks associated with oral erdafitinib and intravesical delivery systems similar to TAR-210 are described below.

Erdafitinib Risks
So far, erdafitinib intravesical delivery system (TAR-210) has not been studied in people, however erdafitinib taken orally has been investigated in several clinical studies and has been approved for treatment of advanced urothelial cancer. As of 11 April 2021, 933 participants have been treated with oral erdafitinib in 18 clinical studies. Safety data from 7 global studies, which enrolled 737 participants with cancer, mostly urothelial cancer, who were treated with erdafitinib, are summarized below. Animals treated with TAR-210 had very low levels of erdafitinib outside of the bladder and did not show any of the side effects described below for oral erdafitinib.

Risks and side effects that could be related to oral erdafitinib include:
Very Common (affects more than 1 out of 10 users))
• Higher than normal levels of phosphate in the blood
• Dryness of the mouth
• Ulcers, blisters or pain in the mouth including cheeks, tongue, or lips
• Diarrhea
• Nail changes and disorders, including nails separating from the nail bed, nail pain, nail bleeding, breaking of the nails, color or texture changes in the nails
• Skin problems including dryness and cracking
• Skin reactions with peeling, redness, swelling tingling or pain in palms of

the hands and soles of the feet, called hand-foot syndrome
• Dryness of eyes
• Redness and irritation of the eye, maybe associated with increased tearing of the eyes, itchy eyes, inflamed eyes
• Loss of hair
• Decreased appetite

Common (affects 1-10 out of 100 users)
• Eye disorders pertaining to fluid build-up under the retina (the light-sensitive layer at the back of the eye) that may or may not be associated with visual symptoms such as blurred or diminished vision or loss of vision
• Infected skin around the nail
• Itching
• Dryness of nose

Most side effects experienced by participants were mild to moderate in severity, and most of the side effects were reversible when oral erdafitinib was stopped. In rare cases, some subjects experienced serious side effects. Because TAR-210 is not expected to deliver as much erdafitinib to the rest of the body as taking erdafitinib by mouth, these side effects may not be seen at all and are less likely to be severe if they do occur.

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

Age 1. >=18 years (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of informed consent. Type of Participant and Disease Characteristics 2. Recurrent, non-muscle-invasive or muscle-invasive urothelial carcinoma of the bladder. a) Mixed histology tumors are allowed if urothelial differentiation is predominant (ie, <20% variant histology). However, the presence of micropapillary, signet ring cell, plasmacytoid, neuroendocrine, or sarcomatoid features are exclusionary. b)High-risk papillary disease (Cohorts 1 [Parts 1 and 2] and 2 [Part 2 only]), defined as histologically confirmed high-grade Ta/T1 lesion. Concurrent CIS is not allowed. All visible tumor must be completely resected prior to the start of study treatment and documented on screening cystoscopy c) Intermediate-risk papillary disease (Cohort 3, Parts 1 and 2) defined as all previous tumors being low grade, Ta or T1, and no previous CIS. Cystoscopic documentation of recurrence is sufficient. Negative urine cytology for high grade urothelial carcinoma is required. Visible disease must be present at the time of first TAR-210 insertion. d) Muscle-invasive disease (Cohort 4, Part 2 only) cT2-T3a, N0. Participants must have a total tumor size <=3 cm after TURBT at cystoscopic assessment within 8 weeks prior to the start of study treatment or must have a second debulking TURBT to reduce the tumor(s) to <=3 cm in order to be eligible. 3. Activating tumor FGFR mutation or fusion, as determined by local* or central testing, approved by the sponsor prior to the start of study treatment: * Local tissue-based results (if already existing) from next-generation sequencing (NGS) or polymerase chain reaction (PCR) tests performed in CLIA-certified or equivalent laboratories, or results from commercially available PCR or NGS tests. 4. Cohorts 1 and 2: BCG experienced, or participants with no BCG experience because BCG was not available as a treatment option in the participant*s location within the previous 2 years and is currently unavailable. Participants who received an abbreviated course of BCG due to toxicity are still eligible. BCG experienced is defined as: - Recurrent high-grade Ta/T1 disease within 18 months of completion of prior BCG therapy - Prior BCG (minimumtreatment requirements): At least 5 of 6 full doses of an initial induction course. Full dose BCG defined as 1 full vial containing a minimum of 1 X 108 colony forming units. Note: Cohort 3 has no predefined prior BCG or intravesical chemotherapy requirement. 5. Cohort 1 only: Refuses or is not eligible for radical cystectomy 6. Cohorts 2 and 4 : willing and eligible for radical cystectomy 7. Cohort 4: Refuses (and understands the risks and benefits of doing so) cisplatin-based combination chemotherapy or is deemed

ineligible for cisplatin-based chemotherapy by meeting at least one of the following criteria: - Creatinine clearance (CrCl)<60 mL/min - NCI-CTCAE v.5.0 Grade >=2 audiometric hearing loss - NCI-CTCAE v.5.0 Grade >=2 peripheral neuropathy 8. Eastern Cooperative Oncology Group (ECOG) performance status score of <=2 (Cohorts 1 and 3)or <=1 (Cohorts 2 and 4)(see Section 10.9 for ECOG scoring) 9. Adequate bone marrow, liver, and renal function: a. Bone marrow function (without the support of growth factors or transfusions in preceding 2 weeks): - Absolute neutrophil count (ANC) >=1,000/mm3 - Platelet count >=75,000/mm3 - Hemoglobin >=8.0 g/dL b. Liver function: - Total bilirubin <=1.5 x the upper limit of normal (ULN) OR direct bilirubin <=1.5 x ULN for participants with Gilbert*s syndrome who have total bilirubin levels >1.5 x ULN - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=2.5 x ULN c. Renal function: - Estimated glomerular filtration rate >30 mL/min calculated using the Modified Diet in Renal Disease (MDRD)formula (see Appendix 11) 10. A female participant of childbearing potential must have a negative serum test at screening and a negative urine test (or serum test if required by local regulations) within 72 hours of the first dose (ie, first insertion)of study treatment, and must agree to further serum or urine pregnancy tests during the study. 11. A female participant must be following contraceptive and barrier (see protocol for elaboration) 12. A male participant must wear a condom(see protocol for elaboration) 13. Must sign an informed consent form (ICF)indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study 14. Willing and able to adhere to the lifestyle restrictions specified in this protocol.

Exclusion criteria

Medical Conditions 1. Concurrent extra-vesical (ie, urethra, ureter, renal pelvis) transitional cell carcinoma of the urothelium. 2. Prior treatment with an FGFR inhibitor. 3. Known hypersensitivity to any study component including: - Erdafitinib (or other drug excipients) or chemically related drugs, - TAR-210 device constituent materials, - UPC materials. Refer to the TAR-210 IB for complete information on excipients, device constituent materials, and UPC materials 4. Received pelvic radiotherapy <=6 months prior to the planned start of study treatment. If received pelvic radiotherapy >6 months prior to the start of study treatment, there must be no cystoscopic evidence of radiation cystitis. 5. Presence of any bladder or urethral anatomic feature that in the opinion of the investigator may prevent the safe placement, indwelling use, or removal of TAR-210. 6. Indwelling urinary catheter. Intermittent catheterization is acceptable. 7. Cystoscopic evidence of bladder perforation unless such perforation has resolved prior to dosing. 8. Bladder post-void residual volume (PVR) >350 mL after second voided urine. 9. History of clinically significant polyuria with recorded 24-hour urine volumes >4,000 mL. 10 Subjects with active bladder stones or history of bladder stones <6 months prior to the start of study treatment. 11. Active malignancies (ie, progressing

or requiring treatment change in the last 24 months) other than the disease being treated under study. Potential allowed exceptions include the following (others maybe allowed with sponsor approval) a. skin cancer (non-melanoma or melanoma)that is considered completely cured. b. non-invasive cervical cancer that is considered completely cured. c. adequately treated lobular carcino main situ(LCIS)and ductal CIS d. history of localized breastcancer and receiving antihormonal agents e. history of localized prostate cancer (N0M0) and receiving androgen deprivation therapy f. Localized prostate cancer (N0M0) - with a Gleason score of 6, treated within the last 24 months or untreated and under surveillance, - with a Gleason score of3+4 that has been treated more than 6 months prior to full study Screening and considered to have a very low risk of recurrence, - or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence. 12. Current central serous retinopathy or retinal pigment epithelial detachment of any grade. 13. History of uncontrolled cardiovascular disease including: - Any of the following within 3 months prior to the start of study treatment: unstable angina, myocardial infarction, ventricular arrhythmias or clinically significant atrial arrythmias (eg, atrial fibrillation with uncontrolled rate), cardiac arrest, or known congestive New York Heart Association Class III-IV heart failure (Appendix 10), cerebrovascular accident, or transient ischemic attack. - Pulmonary embolism or other venous thromboembolism within 1 month prior to the planned start of study treatment. 14. Active or chronic hepatitis B or C infection according to the following criteria: - Seropositive for hepatitis B: defined by a positive test for hepatitis B surface antigen [HBsAg]. Participants with resolved infection (ie, participants who are HbsAg negative with antibodies to total hepatitis B core antigen [anti-HBc] with or without the presence of hepatitis B surface antibody [anti-HBs]) must be screened using real-time polymerase chain reaction (RT-PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are RT-PCR positive will be excluded. Participants with anti-HBs positivity as the only serologic marker AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by RT-PCR. - Hepatitis C infection defined by a positive hepatitis C antibody (anti-HCV) test. Participants who test positive for anti-HCV are eligible if RNA viral load is undetectable (spontaneous recovery or after completing treatment for hepatitis C virus infection). 15. Major surgery within 4 weeks before Day 1 (TURBT is not considered major surgery) 16. Active bacterial, viral, fungal infection, including urinary tract infection*, requiring oral or systemic therapy within 7 days prior to Day 1. *Urinary tract infection is defined as a symptomatic infection with a positive urine culture with a bacterial count of >=10e5 colony forming units (CFU)/mL in urine voided from women, or >10e4 CFU/mL in urine voided from men, or in straight-catheter urine from women. Symptoms may include dysuria, urgency, frequency, and/or systemic symptoms such as fever, chills, elevated white blood cell, and/or abdominal/flank pain. Participants free from symptoms for 7 days with no culture evidence of >10e5 CFUs may be eligible. (See protocol for the remaining exclusion criteria 17, 18, 19, 20, and 21)

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	TAR-210
Generic name:	Erdafitinib

Ethics review

Approved WMO Date:	14-03-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-05-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	08-06-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-06-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-03-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	01-08-2023
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	EUCTR2021-004144-22-NL
CCMO	NL80199.091.22