A phase 1b, Multicenter, Open Label Study Evaluating Safety, Tolerability and Preliminary Efficacy of GemRIS 225mg in Subjects with Non-Muscle-Invasive Urothelial Carcinoma of the Bladder

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The objectives of this study are to:- Evaluate the safety and tolerability of up to 2 dosing cycles of GemRIS for up to 21 days per dosing cycle.- Evaluate the pharmacokinetics of gemcitabine and 2', 2'-difluorodeoxyuridine (dFdU, a...

Ethical review	Approved WMO
Status	Completed
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46132

Source
ToetsingOnline

Brief title
Phase 1b Safety and Tolerability Study of GemRIS in NMIBC

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Non-Muscle-Invasive Bladder Cancer

Research involving
Human

Sponsors and support

Primary sponsor: TARIS Biomedical LLC
Source(s) of monetary or material Support: Industry: TARIS Biomedical LLC

Intervention

Keyword: GemRIS, Urothelial Cell Carcinoma

Outcome measures

Primary outcome

Safety

For GemRIS : Safety of GemRIS upon insertion, two 7-day or 21-day dosing cycles, and removal.

For Custom Inserter : Safety of the Custom Inserter during the placement of GemRIS.

Secondary outcome

GemRIS:

- Tolerability of GemRIS upon insertion, 7-day or 21-day dosing cycles, and removal.

- Pharmacokinetic analysis of blood and urine will be performed : plasma gemcitabine exposure, urinary gemcitabine exposure, plasma dFdU exposure, urinary dFdU exposure .

The following assessments will be performed to determine the anti-tumour effect of GemRIS:

- Assessment of tumour lesion extent (area) at screening cystoscopy compared with cystoscopy on the day of TURBT (prior to TURBT).

- Assessment of tumour cell death as assessed histologically by evidence of

tumour cell apoptosis and necrosis at the time of TURBT.

- Assessment of 2-year recurrence-free survival.

Custom Inserter:

- Tolerability of the Custom Inserter during the placement of GemRIS.

- GemRIS placement success rate as verified by post-insertion cytoscopic

examination.

Study description

Background summary

Worldwide, the prevalence of bladder cancer is estimated to be 2.7 million. In the developing world, the majority of tumours involving the bladder are squamous carcinomas, however, in the developed world, 90% are urothelial carcinomas. The worldwide age standardized incidence (per 100,000 person years) is 8.9 for men and 2.2 for women. In the European Union (EU), the age standardized incidence rate is 27 for men and 6 for women. Since 1975, the incidence of bladder cancer has increased by nearly 40%, largely due to the aging population and its risk factors, including exposure to cigarettes and industrial carcinogens. The majority (75%) of cases are non-muscle invasive bladder cancer (NMIBC), requiring intensive treatment regimens of frequent monitoring, local resection (TURBT, or transurethral resection of bladder tumours), and local intravesical instillation therapies to reduce the risk of both disease recurrence and progression. Despite these efforts, within 5 years from initial diagnosis, 45-61% of patients with NMIBC will experience recurrent disease and nearly 20% of those with high risk disease will progress to muscle invasive tumours requiring radical cystectomy. These demographics illustrate the relatively poor efficacy of current therapies and the significant need for new approaches to bladder cancer. New developments in the management and treatment of NMIBC have been lacking. Therapies like thiotepa (60*s), mitomycin-C (MMC) (70*s), bacillus Calmette-Guerin (BCG) (80*s), and valrubicin (90*s) all suffer from individual shortcomings with respect to efficacy, toxicity, availability and dosing logistics.

Study objective

The objectives of this study are to:

- Evaluate the safety and tolerability of up to 2 dosing cycles of GemRIS for up to 21 days per dosing cycle.
- Evaluate the pharmacokinetics of gemcitabine and 2', 2'-difluorodeoxyuridine (dFdU, a gemcitabine-related metabolite) exposure in urine and plasma during both dosing cycles of GemRIS in both Arms 1 and 2 and the 14-days recovery period between the two GemRIS dosing cycles in Arm 1.
- Determine the preliminary anti-tumour effects of the continuous release of gemcitabine at TURBT in the primary bladder tumour.
- Determine the immunogenic effects of the continuous release of intravesical gemcitabine at TURBT.
- Evaluate the safety and tolerability of the Custom Inserter.
- Evaluate the placement success rate of GemRIS with the Custom Inserter.

Study design

Prospective, multi-center, open-label study of gemcitabine delivered intravesically via TARIS system to subjects with recurrent low or intermediate risk NMIBC between diagnosis and TURBT.

Subjects will be treated with two GemRIS. For Arm 1, the initial GemRIS will be inserted 28 days prior to TURBT and the second will be inserted 7 days prior to TURBT. There will be no delay in TURBT as compared to current standard management of these subjects if they were not participating in this clinical study. For Arm 2, the initial GemRIS will be inserted 42 days prior to TURBT and the second will be inserted 21 days prior to TURBT. The time to TURBT will be extended by 2 weeks. This will allow for additional exposure to gemcitabine that may be resident in the bladder tissue.

Intervention

Patients with recurrent NMIBC (prior history of only low or intermediate risk disease) will be screened following written consent. A cystoscopic examination will have been performed as part of the diagnostic process and the bladders/tumours will be mapped/visually recorded. Patients with a history of high-risk disease (Carcinoma In Situ (CIS), high Grade histology, pathologic stage pT1) will be excluded from the trial. Patients may be screened for up to 21 days before GemRIS insertion.

Arm 1:
On Day 0, subjects who continue to meet inclusion/exclusion criteria will be inserted with GemRIS for 7 days. Urine and blood samples will be collected on pre-specified days while GemRIS is deployed. GemRIS will be removed on day 7. A fourteen-day rest period following GemRIS removal will then lead to a repeat GemRIS insertion on Day 21. The second GemRIS will also remain in place for 7 days. Subjects will again be assessed for safety and tolerability of the investigational product; urine and blood samples will again be collected on

pre-specified days while GemRIS is deployed. A TURBT/Bladder Biopsy will be performed on Day 28, at which time the second GemRIS will be removed. Post-TURBT/bladder Biopsy, there will be a 2 year surveillance period to assess recurrence-free survival.

Arm 2:
On Day 0, subjects who continue to meet inclusion/exclusion criteria will be inserted with GemRIS for 21 days. Urine and blood samples will be collected on pre-specified days while GemRIS is deployed. GemRIS will be removed on day 21 and the second GemRIS insertion will take place. The second GemRIS will remain in place for 21 days. Subjects will again be assessed for safety and tolerability of the investigational product; urine and blood samples will again be collected on pre-specified days while GemRIS is deployed. A TURBT/Bladder Biopsy will be performed on Day 42, at which time the second GemRIS will be removed. Post-TURBT/bladder Biopsy, there will be a 2 year surveillance period to assess recurrence-free survival.

Study burden and risks

GemRIS
Potential risks and benefits will be explained to each potential research participant. The following are potential risks that may be associated with GemRIS.
Common side effects of the GemRIS have not yet been identified as this is a new investigational product, but may include:
* painful urination
* mild blood in urine
* pain in urethra
* abdominal pain
Common side effects of the cystoscopy procedure (may occur more than 10% of the time)
* urinary urgency
* frequent urination
* discomfort as the cystoscope is passed into your bladder for the cystoscopic examination
* discomfort during insertion and removal of the GemRIS device
* discomfort while the GemRIS device is present in your bladder (Arm 1: Days 0-7, Days 21-28 / Arm 2: Days 0-21, Days 21-42)
Common side effects of Gemcitabine (may occur less than 20% of the time)
* bladder irritation (urgency, frequency, pain)
* hematuria (blood in urine)
Uncommon side effects of Gemcitabine (may occur less than 10% of the time)
* neutropenia (abnormally low count of white blood cells, resulting in infection, fever, significant fatigue and easy bruising)
Rare side effects of Gemcitabine (may occur less than 5% of the time)
* allergic reactions, such as itching, hives, facial swelling or difficulty breathing

There are potential risks associated with the same GemRIS in the bladder for greater than the planned placement period. The potential risks may include, but are not limited to:
* Continued delivery of gemcitabine past the 7-day (Arm 1) and 21-day (Arm 2) placement period
* Encrustation (the formation of a hard outer layer) of GemRIS
* Bladder stone formation
* Extensive Cystoscopy to remove GemRIS and/or bladder stone
* Surgery to remove GemRIS and/or bladder stone
* Urinary tract infection
* Blood infection
It is very unlikely that the GemRIS will be expelled from the bladder during this study. In the unlikely event that the GemRIS is expelled during voiding, it can be safely handled with gloves. The GemRIS should be placed in a double plastic bag that will be provided by a member of the study team. The GemRIS should then be returned to the study site at the next office visit.

There is a possibility that the GemRIS may be damaged when passing through the TARIS Inserter. If, on cystoscopic examination following GemRIS insertion, the study doctor believes that the GemRIS may be damaged, it will be removed immediately. However, a damaged GemRIS may be placed into your bladder if the damages are not visible to the study doctor. If this happens, the damaged GemRIS may remain inside your bladder for the duration of 7 or 21 days and it may have no effect, may not work as intended, or may be expelled. If the GemRIS becomes damaged or if it is accidently voided, the study doctor may have to perform some additional tests or procedures, including but not limited to an abdominal x-ray and additional cystoscopy.

The risks of taking blood may include discomfort, fainting, pain and/or bruising (occurring less than 10% of the time). Rarely, there may be a small blood clot or infection at the site of the needle puncture (occurring less than 1% of the time). The band that is placed around your arm while blood is drawn might also cause discomfort or bruising.

The risks from an ECG can include skin irritation and a rash from the gel that is used or from wearing or removing the patches.
GemRIS is an investigational product and has not been evaluated during pregnancy. Pregnant women will not participate in this study. The study doctor will discuss to both male and female participants which methods (and duration) of birth control are acceptable during the study.
The benefits of gemcitabine solution placed directly into the bladder have been demonstrated in previous human clinical trials in subjects with bladder cancer. These benefits include eradication of tumour and delays in the time to tumour recurrence.

TARIS Inserter

Overall the TARIS Inserter has a similar risk profile to existing commercial urinary intermittent catheters. Specifically, the application risks include one significant risk: the potential for tissue damage as the shaft is navigated through the urethra in certain patients with compromised anatomy (e.g. enlarged prostate, weakened or affected tissue due to previous transurethral procedures). This is a procedural risk that is present for any urinary catheterisation procedure and is not specific to, nor elevated for, the TARIS Inserter. This risk will be managed during the study by excluding patients with any bladder or urethral anatomic feature that in the opinion of the study doctor may prevent the safe placement, indwelling use or removal of GemRIS.

Overall, due to lack of any clinical experience with GemRIS and the TARIS Inserter, risk factors cannot be assessed in more detail at this time. The safety of the research participants is the primary objective of this study and adequate monitoring and guidance for stopping criteria have been incorporated into the protocol to minimise risks associated with GemRIS and the TARIS Inserter

Contacts

Public
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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. Age * 18 years at the time of consent.
2. Able to voluntarily give written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
3. A documented history of histologically-confirmed low or intermediate risk urothelial carcinoma of the bladder, excluding carcinoma in situ (pTis), pathologic stage pT1 (invasive into lamina propria) and high-Grade disease, judged not to be muscle infiltrating (pT2 or greater) and accessible for resection.
4. Females of childbearing potential must have a negative pregnancy test.
5. Acceptable liver function defined as: bilirubin * 1.5 times upper limit of normal, and aspartate aminotransferase (AST) (SGOT), alanine aminotransferase (ALT) (SGPT), and alkaline phosphatase * 2.5 times upper limit of normal.
6. Acceptable renal function defined as calculated creatinine clearance * 0.58 mL/s/m2 (35 mL/min/1.73 m2).
7. Acceptable hematologic status defined as: absolute neutrophil count (ANC) * 2.5 x10^9/L (2,500 cells/mm3), platelet count * 120 x10^9/L (120,000/mm3), and hemoglobin * 6.21 mmol/L (10.0 g/dL).
8. Screening urinalysis showing no clinically significant abnormalities except those attributable to bladder cancer.
9. Not undergoing active treatment in last 3 months for prior or concurrent neoplastic disease and have fully recovered from treatment effects. Subjects undergoing concurrent hormonal therapy treatment for prostate cancer will be allowed to enroll.
10. Females of childbearing potential must be willing to use an effective method of contraception (hormonal or barrier method of birth control; abstinence) from the time consent is signed until 4
weeks after treatment discontinuation. Subject*s partner must also use barrier protection while subject is on study until 4 weeks after treatment discontinuation.
11. Males must be willing to use an effective method of contraception/method to avoid seminal transfer (barrier method or abstinence) from the time consent is signed until 4 weeks after treatment discontinuation. Subject*s partner(s) must also use barrier protection while subject is on study until 4 weeks after treatment discontinuation.

Exclusion criteria

1. Exposure to BCG therapy and/or any other intravesical chemotherapeutic agent less than 1 year prior to enrollment, except single postoperative instillations.
2. Absence of visible tumour at Screening.

3. Any previous exposure to intravesical gemcitabine instillations within the last 12 months.
4. Presence of any bladder or urethral anatomical feature that in the opinion of the Investigator may prevent the safe placement, indwelling use or removal of GemRIS (i.e. bladder diverticula,
complete incontinence).
5. Documented history of vesicoureteral reflux or an indwelling ureteral stent or nephrostomy tube.
6. Subjects with a high-Grade urine cytology at recurrence.
7. Currently receiving other systemic or intravesical chemotherapy.
8. Evidence of bladder perforation during diagnostic cystoscopy.
9. Pelvic radiotherapy administered within 6 months prior to enrollment. Subjects who received radiotherapy * 6 months prior to enrollment must demonstrate no cystoscopic evidence or
clinical symptoms of radiation cystitis.
10. Bladder Post-Void Residual Volume (PVR) of > 250 mL.
11. Known hypersensitivity to gemcitabine or chemically-related drugs.
12. Known hypersensitivity to the device materials.
13. Active, uncontrolled urogenital bacterial, viral, or fungal infections, including urinary tract infection. Skin/nail fungal infections are not exclusionary. Subjects with active shingles (varicella zoster infection) will be excluded from the study.
14. Use of an investigational agent within 30 days or 5 half-lives, whichever is longer, preceding Study Day 0.
15. History or presence of any significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, gynecological, endocrine, immunological, dermatological, neurological or psychiatric disease or disorder that, in the opinion of the Investigator, contraindicates participation.
16. History of a diagnosis of neurogenic bladder.
17. Concomitant immunosuppressive medications, such as methotrexate or TNF inhibitors, within 2 weeks of Study Day 0, exclusive of steroid doses * 5 mg daily.
18. History of any of the following within 3 months prior to the date of informed consent:
a. Major illness/major surgery (requiring hospitalization), including pelvic, lower back surgery or a procedure unrelated to bladder cancer; most outpatient procedures are not exclusionary
b. Renal or ureteral stone disease
c. Childbirth
19. Female subject who is pregnant (as verified by urine test at time of screening) or lactating or of childbearing potential and not using acceptable methods of contraception.
20. Difficulty providing blood samples.
21. Clinically significant abnormal complete blood count (CBC), blood chemistry or urinalysis at the Screening Visit that is verified upon repeat testing.
22. Unwilling or unable to provide informed consent or comply with the requirements of this protocol, including the presence of any condition (physical, mental or social) that is likely to affect the subject*s return for scheduled visits and follow-up.
23. Other unspecified reasons that, in the opinion of the Investigator or TARIS, make the subject unsuitable for enrollment.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	27-07-2016
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	TARIS Inserter
Registration:	No
Product type:	Medicine
Brand name:	not available
Generic name:	not available

Ethics review

Approved WMO Date:	24-03-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-07-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-09-2016

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-03-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-10-2017

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-05-2020
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	EUCTR2016-000099-66-NL
CCMO	NL56783.091.16

Study results

Date completed:	03-03-2020
Results posted:	03-03-2021

First publication
22-02-2021