Observation Plan on the use of tissue-engineered autologous Implants of the Oral Mucosa (MukoCell®) in Reconstruction of the Urethra

Final version 3.0, 30 April 2012 (incorporating Amendment 1 of 30 April 2012)

Replaces Final version 2.0 of 16 May 2011

1 Table of Contents

Figures

2 Persons and Institutions Involved in the Observation

Pharmaceutical entrepreneur	UroTiss GmbH Budapester Str. 3 01069 Dresden Phone: +49(0)351/438 32 999 Fax: +49(0)351/438 32 997 E-Mail: info@urotiss.com
Lead Contact of Pharmaceutical entrepreneur	[redacted] UroTiss GmbH Budapester Str. 3 01069 Dresden [redacted]
Evaluation of Data	[redacted] UroTiss GmbH Budapester Str. 3 01069 Dresden [redacted]
Scientific Advice, Biometrical Concept, Amendment 1	[redacted] Diploma Pharmaceutical Medicine (DGPharMed) Erwinstraße 35 79102 Freiburg [redacted]
Involved urologist/clinical institution	[redacted] Uro-Forschungs GmbH im St. Hedwig Krankenhaus Große Hamburger Strasse 5-11 10115 Berlin [redacted]

Introduction

Any inflammation of urethra can result in scarring which then can lead to a stricture or a narrowing of the urethra. Scar tissue contracts and reduces the calibre of the urethral lumen, causing resistance to the antegrade flow of urine.

Urethral stricture is significantly more common in men compared to women. This condition is considered rare in females (Wong et al 2010, Lumen et al 2009).

The most important causes of urethral stricture are idiopathy, transurethral resection, urethral catheterization, pelvic fracture and hypospadias surgery. Overall iatrogenic causes (transurethral resection, urethral catheterization, cystoscopy, prostatectomy, brachytherapy and hypospadias surgery) are the etiology in 45.5% of stricture cases. In patients younger than 45 years the main causes are idiopathy, hypospadias surgery and pelvic fracture. In patients older than 45 years the main causes are transurethral resection and idiopathy. In cases of penile urethra hypospadias surgery, idiopathic stricture, urethral catheterization and lichen sclerosus are the main causes, while in the bulbar urethra idiopathic strictures are most prevalent, followed by strictures due to transurethral resection (Lumen et al 2009). Santucci et al 2007 report about a clear trend of increasing incidence of urethral stricture with age, while mostly an increase of this disease in patients older than 55 years is represented in his study.

Urethral strictures are diagnosed based on suggestive history, findings on physical examination, imaging contrast studies (retrograde urethrogram or anterograde cysto-urethrogram if the patient has an existing suprapubic catheter) and endoscopic evaluations (cysto-urethroscopy). The entire urethra, both proximal and distal to the strictured area, must be evaluated endoscopically and/or radiographically prior to any surgical intervention.

The majority of stricture patients suffer from moderate complications such as irritative voiding symptoms, recurrent urinary tract infections (41%), incontinence (11%), or the need for repeated urethral procedures (e.g., dilation or urethrotomy). A minority suffer from severe sequelae such as acute urinary retention, renal failure, urethral carcinoma, or bladder failure resulting from long-standing obstruction (Santucci et al 2007).

There are essentially no medical treatments (medications) for urethral strictures other than those offering symptom control (for example pain medications to control discomfort). Early treatment of urethritis or urinary tract infections with antibiotics is important in this matter. The treatment of urethral strictures can be divided into two main categories:

1. Non-operative (intermittent self-catheterization or suprapubic catheter for long-term management, periodic urethral dilations), symptomatic medical treatment for pain. Surgery remains the only treatment for individuals with uncontrolled symptoms of urethral narrowing.

2. Operative therapy: The primary standard operative therapy of urethral stricture is the minimally invasive/endourological (internal urethrotomy) procedure. This has a success rate of about 50%. The success rate of urethrotomy is declining in patients with re-strictures and strictures appear to re-occur in shorter periods of time (Heyns et al 1998, Santucci et al 2007, Santucci and Eisenberg 2010). Alternatively, an open surgical reconstruction (urethroplasty with excision of the fibrotic urethral segment with tissue-transfer techniques) is recommended in patients having failed previous urethrotomies (Wong et al 2010, Naude et al 2005, Heyns et al 1998, Steenkamp et al 1997).

The surgical therapy of urethral stricture is recommended in case of low urinary flow rate, severe problems with urination and urinary retention, kidney stones in the bladder, recurrent urinary tract infections, increasing amount of urine left in bladder after urination (post-void residual), failure of conservative measures to control pain and failure of previous non-operative treatments.

In open surgical tissue transfer techniques the most common tissue that is used to aid in reconstruction is buccal mucosa, taken from the inside lining of the cheek or lower lip and grafted into the urethra. This allows the surgeon to develop a more wide open urethra (Markiewicz et al 2007, Jang et al 2005, Mehrsai et al 2007, Wong et al 2010, Bhargava and Chapple 2004).

The standard surgical treatment for the majority of patients with urethral stricture is currently urethrotomy. However, in some centres urethroplasty using mucosal oral transplants is performed mainly in patients who have failed previous urethrotomy treatment (Markiewicz et al 2007). Concluded from a bulbar urethroplasty cohort of 20 patients receiving buccal mucosa the success rate for inflammatory strictures was 75% and for iatrogenic and others 80% and 81% respectively during a mean post-surgery follow-up of 13 months (Meneghini et al 2001). Recipient site complications such as fistula formation, meatal stenosis and graft contracture generally occur during the first postoperative months.

Complications at the oral donor site occur very frequently. The vast majority of patients suffer from early complications such as oral pain, peri-oral numbness and oral tightness. Late or permanent complications in the oral cavity are still very frequently oral tightness/restriction of mouth opening (9-32%), peri-oral numbness (16-26%) and frequently occurring hyposensitivity/paraesthesia (2-3%), which imposes a heavy (oral) burden on the patient (Wood et al 2004, Dublin and Steward 2004, Dubey et al 2007, Jang et al 2005, Heinke et al 2003, Mehrsai et al 2007).

Apart from this complications presented above oral contracture is a devastating complication reported in 3-26% of patients after lip graft harvest.

UroTiss provides as the first company an autologous oral mucosa engineered transplant from an oral mucosal biopsy (MukoCell®) for reconstruction of the urethra. Oral complications observed with native oral mucosal are not expected with MukoCell® where an oral mucosal biopsy is needed only.

MukoCell® is an advanced therapy medicinal product according to Regulation (EC) No 1394/2007 of the European Parliament and of the Council. Due to the regulation No. 1394/2007 of European Parliament and the council, MukoCell® is on the market since December 2008 and can be marketed for a transition period until 30 December 2012 without further authorization. In Germany an even longer transition period according to section 4b of the German Drug Law may apply.

3 Rationale of this Observational Study

3.1 Aim of the Observational Study

MukoCell® has been used in patients undergoing oral surgery. In the case of urethral stricture no systematic investigation has been done, so far with MukoCell®. This observation plan will be conducted to gather further information concerning the clinical use of MukoCell® in treating stricture of the urethra.

The aim of this observation is

- to gain knowledge about potential adverse reactions during routine application of MukoCell®;
- to expand knowledge about the efficacy (i.e. treatment outcome at 3, 6, 12, 18, and 24 months after urethral surgery) of using MukoCell® under routine conditions for urethroplasty in patients with urethral stricture;
- to gain knowledge about prescription behavior and prescribing habits, compliance to the summary of product characteristics.

This observational plan has been developed to investigate the clinical use of MukoCell® and its effects in patients with urethral stricture. The results of this observation will support to plan further clinical studies and to support the data package for regulatory approval.

It is deemed realistic to obtain data of at least 100 evaluable patients within two years, a period reasonable for the collection of data for the planning of following studies. A number of at least 100 patients is assumed to allow to obtain a robust expertise regarding the clinical use of MukoCell® and its medium term outcome. A formal sample size calculation to gain knowledge on the true outcome 12 months after the intervention has been performed (refer to 8.1).

3.2 Variables of Interest

3.2.1 Demographic and Disease Specific Variables

- Age, gender, ethnicity, height, weight, smoking habits
- Vital signs (temperature, arterial blood pressure, heart rate)
- Urinary symptoms and signs (difficulty starting urinary flow, painful urination, obstructive voiding symptoms, urinary retention, urinary tract infection, bladder calculi, residual urinary volume)
- Urologic examinations (passageability of urethra with a 16-18 French catheter, uroflowmetry, (cysto)-urethroscopy, urethrography)
- Localization of stricture including method of assessment, number of previous urethral strictures, date/year of first stricture, number of previous vesico-urethral

infections, types of interventions (urethrotomy, urethral dilation, open urethral surgery)

- Ethiology of the stricture
- Drug history (up to 4 weeks prior to urethroplasty) and concomitant medication
- Perioperative antibiotic prophylaxis or treatment / antibiogram
- Previous and concomitant diseases
- Oral biopsy procedure (date, anti-HIV 1/2 HBs-Ag, anti-HCV, and TPHA tests in blood, duration of shipping [biopsy and blood] from excision site to laboratory)

3.2.2 Primary Outcome Variable

- 'Success rate' of urethroplasty procedure with MukoCell® at 12 months, which is defined by the absence of stricture recurrence.

A re-stricture is defined based on routine medical care at the participating site as postoperative peak flow rate < 15 ml/s and urethra is not passable with a 16-18 F catheter into the urinary bladder or during standard urethroscopy under visual control.

3.2.3 Secondary Outcome Variables

- Treatment success at 3, 6, 18, and 24 months after MukoCell® urethroplasty
- Spontaneous urination
- Uroflow (Peak flow)
- Spontaneous urination of the treated patient 24 hours after removal of the intraoperatively inserted catheters will be observed (Spontaneous urination will be evaluated as success).
- Patient's urethral and oral pain and well-being (Likert scale)

3.2.4 Safety Variables

- Adverse reactions (related to MukoCell®)
- Complications at oral and urethral site
- Physical examination
- Vital signs
- ECG
- Laboratory parameters (clinically relevant deviations indicated by physician)

For the evaluation of safety, data about unusual irritations of the urethra and the surgical site, incompatibility or rejection reactions and other adverse reactions

considered to be related to the use of MukoCell® will be collected. Oral adverse reactions after mucosal biopsy and perioperative complications will be observed as well.

Routine follow-up visits after urethroplasty may vary between observational sites. Available follow-up information is assigned to the closest available assumed routine follow-up visit. Visits ± 6 weeks outside the assumed follow-up visits can be documented as an additional visit.

3.3 Patient Population

Participating investigators will treat patients according to their medical practice. If he/she thinks that patients qualify for a treatment with MukoCell®, he/she will include patients who ideally fulfill the following criteria:

- Informed consent
- Male patients at the age between of 18 – 85 years
- Urethral stricture
- Oral biopsy for MukoCell® production

Since this is an exploratory observation, no special measures for representative selection of patients and medical doctors are planned. However urethroplasty is currently practiced in some urologic centres in Germany and this non-interventional study will be (has been) placed in several centres, which appears a representative sample of centres carrying out urethroplasty procedures and of the targeted patient population currently receiving (native) urethroplasty in Germany.

4 Observation Schedule

All data captured during the observation must be obtained from routine clinical care assessments which must be done by the investigators according to their medical practice. No additional examinations or clinic visits will be done. The treatment with MukoCell® has to be done according to the given conditions without any restrictions. The results of pre- and post-operative radiologic examinations, obtained from routine clinical care will be documented in the CRF.

4.1 Before Urethroplasty

Before use of any personal data for the purpose of this observation the participating patients must give their consent. The demographic data, data from anamnesis, physical examination, measurement of vital signs, information about medical history and concomitant medications, which are collected during the routine examinations before the operation procedures, will be recorded in the case report forms (CRF). The check of the inclusion criteria will be entered into the CRF. If urethroscopy and / or retrograde urethrography / miction cystourethrograpy and / or uroflowmetry are performed, the results of these methods will be recorded in the CRF. Additionally, if available, further information regarding the localization of the stricture, the ethiology of the stricture, previous recurrences and treatments will be recorded in the CRF. If an ECG is performed, the results are recorded in the CRF.

According to the procedures prescribed for the preparation of MukoCell®, sampling of oral mucosa biopsy will be done and blood samples will be obtained to obtain autologous serum. This will be recorded in the CRF. All samples will be sent to BioTissue Technologies GmbH, Freiburg. The harvest of the biopsy and blood and their transport to BioTissue Technologies GmbH are validated procedures and are part of the manufacture authorization of MukoCell®. Blood will be analyzed for antibodies against HIV1/2, HBs-Ag, anti-HCV and TPHA. Information about concomitant medications obtained at the day of the biopsy will be documented in the CRF.

The surgical reconstruction of the urethra will include the implantation of MukoCell®. This will be recorded in the CRF. According to the procedures prescribed for the use of MukoCell®, one or two permanent catheters will be inserted for the diversion of the urine in the urinary bladder and in the urethra. Treatment date, vital signs, results of physical examination, complications, concomitant medications, adverse reactions considered to be related to the use of MukoCell®, and relevant observations of the investigator will be documented in the CRF. If an ECG is performed, the results are recorded in the CRF.

4.2 After Urethroplasty

Early post-implantation examinations will be scheduled according to medical practice. Usual time points are 1 and 7 days after the implantation. The patients will receive standard postoperative treatment. If the investigator questions the patient about pain and subjective well-being, the answers will be recorded in the CRF. If the wound is controlled and if uncompromised healing or complications are found, the observations will be documented in the CRF. If a physical examination is performed and vital signs are measured, the data will be recorded in the CRF. If blood parameters are examined, this will be documented in CRF. Also the dates of the examinations, complications, compliance, adverse reactions considered to be related to the use of MukoCell®, concomitant medications and relevant observations of the investigator will be documented in the CRF.

Late post-implantation examinations will be scheduled according to medical practice. A usual time point is 10 days after the implantation. The patients will receive standard postoperative treatment. If the investigator questions the patient about pain and subjective well-being, the answers will be recorded in the CRF. If the wound is controlled and if uncompromised healing or complications are found the observations will be documented in the CRF. The dates of the examinations, adverse reactions considered to be related to the use of the MukoCell®, concomitant medications, compliance and relevant observations of the investigator will be documented in the CRF.

The removal of transurethral catheter and suprapubic catheter will be scheduled according to medical practice. This will be documented in the CRF. A usual time point for urethral catheter removal is 3-28 days after the implantation. If the wound is controlled the observations will be recorded in the CRF. If the investigator questions the patient about pain and subjective well-being, the answers will be recorded in the CRF. The date of the removal of transurethral catheter and suprapubic catheter, complications, compliance, adverse reactions considered to be related to the use of MukoCell®, concomitant medications and relevant observations of the investigator will be documented in the CRF.

First examination after catheter removal will be scheduled according to medical practice. Usual time point is 2±1 day after catheter removal. If a urinary stream measurement (uroflowmetry), retrograde urethrography / miction cystourethrograpy, urine culture, wound inspection is performed, the observations will be recorded in the CRF. If urethro-cystoscopic examination is performed, this will be documented in CRF. If the patient is questioned about pain and subjective well-being, the results will be recorded in the CRF. The dates of the examinations, complications, information about compliance, adverse reactions considered to be related to the use of MukoCell®, concomitant medications and relevant observations of the investigator will be documented in the CRF.

Follow up examinations will be scheduled according to medical practice. Usual time points are 3, 6, 12, 18 and 24 months post implantation. If a urinary stream

measurement (uroflowmetry), retrograde urethrography / miction cystourethrograpy, urethro-cystoscopy, urine culture, wound inspection is performed, the observations will be recorded in the CRF. If the patient is questioned about pain and subjective well-being, the results will be recorded in the CRF. The dates of the examinations, complications, information about compliance, adverse reactions considered to be related to the use of MukoCell®, concomitant medications and relevant observations of the investigator will be documented in the CRF.

The planned observations at the corresponding time intervals (expected routine follow-up visits) are shown in Table 1. An observation visit may include several days of observation.

Table 1: Schedule of Planned Observations

	Pre-Urethro-plasty	Urethro-plasty	Post-Op	Removal of catheter	2±1 day post catheter removal	Post-Urethroplasty Follow-Up				
Collected Data of Estimated Observation	W -3±1	D1	D2	D3-28		M3	M6	M12	M18	M24
Informed consent	x									
Demographics (date of birth, ethnic origin, weight, gender, height, smoking)	x									
Urinary symptoms and signs, lengths of stricture, stricture history (first stricture, number, intervention types, urinary infections)	x	(x)								
Oral biopsy + plasma sample + infectious status	x									
Eligibility criteria	x									
Periopative antiinfective treatment or prophylaxis / antibiogram	x	x	x	x		x				
Uroflow / spontaneous micturition	x	x		x	x	x	x	x	x	x
Re-stricture assessed by urethrography, urethroscopy, uroflow, passageability for 16-18 French catheter (optional via phone, email)	x			x	x	x	x	x	x	x
Self-assessment patient (oral, urethral pain, well-being)		x	x	x	x	x	x	x	x	x
Adverse reaction (ADR) to MukoCell® (at least possibly related)		x	x	x	x	x	x	x	x	x
(Peri-operative) complications at oral and urethral site	x	x	x	x	x					
Physical examination	x	x	x	x		x	x	x	x	x
Vital signs	x	x	x	x		x	x	x	x	x
ECG	x			x						
Laboratory parameters (clinically relevant deviations)	x	x	x	x		x	x	x	x	x
Previous / concomitant disease and medication	x	x	x	x		x	x	x	x	x
Final Observation Form (earlier in case of re-stricture, ADR until 2 years)						(x)	(x)	(x)	(x)	x

Note: All data planned to be collected around the estimated time periods are usually available from routine / standard clinical assessment. This is a non-interventional study. Therefore no medical interventions or assessments will be done for the purpose of this 'observational schedule'. If assessment were not performed on routine clinical grounds this will be documented as 'NA' meaning 'not assessed' in the CRF.

Routine visits should be assigned to the closest suggested follow-up visit, optional additional observation visits are provided in the CRF.

5 Recording of Adverse Reactions and Reporting of Serious Adverse Reactions

For this observation an adverse reaction is defined as a response to MukoCell®, which is noxious and unintended. The phrase "response to MukoCell®" means that a causal relationship between MukoCell® and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All adverse reactions involving the use of MukoCell® will be recorded in the CRF.

Serious adverse reaction is any untoward medical occurrence or effect that at any dose

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation,
- results in persistent or significant disability or incapacity.

Note: The implantation surgery will not be regarded as adverse reaction.

Prolongation of hospitalisation after MukoCell® urethroplasty will not be recorded as serious adverse event

Any serious adverse reaction is to be reported by the investigator to UroTiss GmbH immediately. The investigator will be requested to supply as much detailed information as possible regarding the serious adverse reaction that is available at the time of the initial contact. A serious adverse reaction reporting form is provided in the investigator file. The investigator is also required to complete missing or requested information and to submit follow-up reports to UroTiss GmbH until the serious adverse reaction has resolved or, in the case of permanent impairment, until the serious adverse reaction has stabilized.

UroTiss GmbH will further be responsible for reporting all serious adverse reactions as soon as possible to the appropriate authorities, as required by applicable law.

6 Case Report Form (CRF)

Special case report forms will be developed to ensure the correct entry of patients' data as well as examination results. A CRF must be completed for each patient. CRFs have to be filled in with black ball pens and shall be legible and complete. It is the investigator's responsibility to ensure completion and consistency with the patient chart and to review and approve all data entered. When making corrections to the CRF, the original entry must not be obscured. Any change or correction must be dated and signed, or initialed, by the person making the corrections. The original completed and signed CRF pages will be sent to the organization assigned by UroTiss GmbH for processing of data.

The observation plan and the CRF have been created to collect data for comparison. If routine practices for data collection contradict parts of the observation plan, the routine practices should be conducted. This will be recorded in the CRF. Other deviations from the observation plan should also be documented in the CRF.

7 Monitoring and Quality Assurance

To ensure the data quality at least one monitoring visit by a monitor will take place to check for completeness and validity of data. Source data verifications of at least 10% of included patients will be conducted. Depending on the number of findings / discrepancies the monitoring frequency and the source data verification may be intensified.

Case report forms will be entered into a database and reviewed by qualified data management personnel for omissions, apparent errors or values requiring further clarification.

The data will be checked for accuracy and consistency by running a series of validated plausibility-check programs. An additional visual check will be performed to assure the medical plausibility of the data.

If necessary, questions (queries) identified will be addressed to the investigator for resolution on special query forms. The investigators will answer the questions directly on the query forms and send them back signed and dated to the data management. Corrections will be entered by the data management into the database. The database will be locked after the resolution of all queries. This will be documented.

8 Statistics

8.1 Sample Size Calculation

The precision (width) of the 95% CI for the true proportion of the success rate / outcome of the urethroplasty procedure with MukoCell® is used to justify the sample size of the cohort.

Using the formula (National Statistical Service 2011, Matheboard 2011)

$$n = 4z^2_{1-\alpha/2}\frac{p(1-p)}{d^2}$$

n=required sample size, z-value of normal distribution, α = alpha error, d=widths of 95% confidence interval, p= outcome

a sample size of evaluable 100 patients is needed for a precision d = 0.18 (18%) based on an estimated treatment success of p=70% (at 12 months post urethroplasty procedure) and an two-sided α of 0.05, which corresponds to a 95% probability that the (true) population outcome rate p is within the limits of the 95% confidence interval. The sample size of 100 patients is also supported by the calculation of distribution independent tolerance limits, where 93 patients are required to establish the 95% confidence interval for the population outcome rate (Sachs and Hedderich 2006).

Considering a lost to follow-up rate of approximately 20% at least **120 patients** should be included into this observational cohort. Lost to follow-up patients are patients where no 12 months follow-up information is available. The number of observed patients may be increased correspondingly if the lost to follow-up rate is exceeding 20%.

The estimated treatment success is based on a published study on native (oral mucosa) urethroplasty outcome (Meneghini et al 2001).

For patients not returning to the surgical site for routine follow-up physicians may collect information on outcome via the local urologist or treating physician. This procedure, if any, is documented in the CRF.

8.2 Patient Analysis Sets

All Patients Treated Set – Full Analysis Set (FAS)

All patients who received MukoCell® during the urethroplasty procedure will be included.

Patients who had oral biopsy only (and no MukoCell® urethroplasty) will not be included in the FAS but shown separately, in case information is available.

The FAS set is also identical to the safety analysis set.

Complete Follow-up Set

All patients who received MukoCell® urethroplasty and where 12 months follow-up information on outcome (re-stricture yes or no) is available are included in the complete follow-up set.

Pre-treatment (baseline) variables such as demographics, medical history, ethiology, stricture localisation and stricture disease characteristics will be presented using descriptive statistical methods.

8.3 Efficacy Analysis

The recurrence of the stricture should be measured by common urologic diagnostics at the time-points three, six, twelve, eighteen, and twenty-four months postoperative and will be evaluated by the investigator. This evaluation is also a “yes” or “no” decision. The absence of a stricture recurrence will be regarded as success of the treatment. The criteria for a diagnosis of stricture-recurrence for the primary outcome variable are described in Chapter 3.2.2).
The 95% confidence interval (proportion) will be calculated for the primary outcome variable ‘treatment success’ at 12 months post MukoCell® urethroplasty.
Secondary outcome variables
Treatment success at other time points – presentation of treatment success (proportion) over time including 95% confidence intervals
Spontaneous urination after the removal of the intraoperatively inserted catheter will be evaluated by the investigator. This is a “yes” or “no” decision. Spontaneous urination will be evaluated as success.
Values for all secondary efficacy parameters such as uroflow, spontaneous micturition, passageability for 16-18 French catheter, pain at urethral and oral site, and well-being (refer to Chapter 3.2.3) will be analysed with descriptive statistical methods.

8.4 Safety Analysis

Safety will be evaluated by the documentation of unusual irritations of the urethra and the surgical site, incompatibility or rejection reactions and other adverse reactions considered to be related to the use of MukoCell®, complications at the oral

site, physical examination, vital signs, ECG (normal / abnormal), and clinically relevant deviations of laboratory parameters as indicated by the physician (refer to 3.2.4). These adverse reactions will be summarized and provided as data listings and summary tables. Verbatim terms will be mapped to preferred terms and organ systems using the Medical Dictionary for Regulatory Affairs (MedDRA). For each preferred term frequency counts and percentages will be calculated.

8.5 Further Data Analyses

All continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, median, minimum, maximum, 25th percentile, and 75th percentile). Summary statistics for categorical variables will include frequency counts and percentages. Summaries will be presented for all patients.
Data will be analyzed by using a statistical software package. Detailed analyzing procedures are described in the statistical analysis plan.

9 Regulatory and Ethical Aspects

9.1 Patient Consent to Use of Health Data

Patients must consent in writing to the collection and use of their health data for this observation. For this purpose, two copies of the informed consent forms must be signed and dated by the patient and must be countersigned by the investigator who explained to him the nature, aims and methods of the observation. One signed informed consent will be handed out to the patient, and the second will remain in the investigator's study file.

The informed consent will be updated to include changes covered by Amendment 1 (incorporated in Final version 3.0). These are mainly the extension of the individual observation from 6 months to 24 months, the agreement of the participating patient that the physician (or delegate) at the study site performing the urethroplasty may collect follow-up information from the treating urologist / physician close to the patient's home to obtain follow-up information, and the conduct of additional monitoring (at the site) as well as the possibility of audits or inspections to ensure data quality.

No data can be collected for this observation before the written informed consent is obtained. Participating patients have the right to withdraw consent to the use of their data for this study at any time and without naming a reason. This decision must not have any impact on further treatment.

9.2 Data Protection

Collection, transmission, recording and analyses of personal data will be done according to the national data protection laws. The premise is the voluntary acceptance of the participating patient, documented on the informed consent form.

The patient data will be forwarded to UroTiss GmbH only in pseudonymous form. It is the responsibility of the investigator to ensure that there are no names on CRFs or any other documents forwarded to UroTiss GmbH. Documents will be identified solely by a subject identification number. This also applies to all statistical analyses, which will only be based on patient numbers, without identifying any names. If, for medical reasons, it becomes necessary to identify the name of a patient, all persons involved are obliged to maintain strict confidentiality.

9.3 Notification Procedures

In Germany, the national association of statutory health insurance physicians (Kassenärztliche Bundesvereinigung), the central association of the health insurances (Spitzenverband Bund der Krankenkassen) and the competent authority (PEI) will be notified according to legal requirements.

9.4 Independent Ethical Committees

Local regulations and requirements for the involved sites or physicians will be followed strictly. Participating physicians will consult their local ethical committee, if required, prior to participation.

10 Reports

A final report will be prepared by UroTiss GmbH or an authorized designee. The report should contain the items to be addressed in reports of observational studies according to the STROBE Statement (von Elm et al 2007) and will at least partly follow the form and content of clinical study reports according to ICH E3 guideline. A final report will be prepared regardless of whether the study is completed or prematurely terminated. A summary of the report will be provided to the investigators following finalization of the report. 12 months follow-up data of at least 100 patients are reported first. 24 months follow-up data are reported in an addendum report or as an updated report of the 12 months follow-up data.

11 Signature Page

The signatories have read this observation plan and declared their agreement to carry out the observational study in accordance with this observation plan. UroTiss GmbH must be informed immediately in case of changes in responsibilities.

UroTiss's responsible person

_____ _____

Name, first name (in printed characters) Date, Signature

Investigator

By signing this observation plan I, the Investigator, confirm that I have read and understood the observation plan, and that I assume responsibility for conducting the observational study according to this observation plan.

_____ _____

Name, first name (in printed characters) Date, Signature

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