CLINICAL INVESTIGATION PLAN

TIES® C03 Study

Prospective multicentre open clinical study to assess the safety performance and durability of the TIES® transcutaneous titanium implant in patients requiring a permanent ileostomy

Protocol No	**TIES® III C03**
Version	5.0
Date	02 Feb 2022
Sponsor	**OstomyCure AS** Oslo, Norway

EXCLUSIVELY FOR CLINICAL INVESTIGATION

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Person or organization that takes responsibility for the initiation and / or the implementation of a clinical investigation:

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CLINICAL INVESTIGATION ORGANIZATION

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PROTOCOL SIGNATURE PAGE

PROTOCOL NUMBER: TIES® C03 STUDY

Prospective multicentre open clinical study to assess the safety performance and durability of the TIES® transcutaneous titanium implant in patients requiring a permanent ileostomy

I have read the Clinical Investigation Plan mentioned above and agree to adhere to its requirements.

I have received a copy of the most current version of the Investigator's Brochure.

I will provide copies of the Protocol and access to all information furnished by OstomyCure ("Sponsor") to the study personnel under my supervision and involved in carrying out the study. I will discuss this material with them to ensure that they are fully informed about the investigational device and the conduct of the study.

I have read the Confidentiality Statement of this Protocol. The contents of this Protocol may not be used in any other clinical study and may not be disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by law or regulation, for example submission to an Ethics Committee; however, I will give prompt notice to the Sponsor of any such disclosure.

Site Number/Name: _____

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Date: _____ Signature:

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Date: _____ Signature:

CLINICAL INVESTIGATION PLAN

PROTOCOL SYNOPSIS

Title:	Prospective multicentre open clinical study to assess the safety performance and durability of the TIES® transcutaneous titanium implant in patients requiring a permanent ileostomy
Protocol Number:	TIES® III C03
Medical Device:	TIES® (Transcutaneous Implant Evacuation System)
Study Design:	This is a prospective open multi-center clinical study that evaluates the safety, performance and durability of the TIES® transcutaneous titanium implant (TIES® Port) to 12-months post implantation. A minimum of 200 patients from up to 25 sites will be enrolled in the study. The study population includes patients requiring a permanent ileostomy; or patients with a medical need for an alternative to an existing conventional ileostomy, continent ileostomy or pelvic pouch. This protocol plans for five interim data analyses. The first two interim analysis are planned after collection of 8-week results from the first 5 and of 24-week results of the first 20 subjects respectively, to review all available study data and to assess if there is a need to modify the study protocol including adjusting the collection of outcome measurements for performance assessment. The third, fourth and fifth interim analyses will be conducted when 50, 100 and 150 subjects, respectively, have completed 24 weeks follow-up in order to assess the primary and secondary 24-week safety and performance endpoints, make a preliminary assessment of the types of patient with high device acceptability, and consider whether some of the secondary study instruments (e.g. Quality of Life Questionnaires) can be dropped for the remaining patients to simplify follow-up and reduce burden on patients and clinical teams. This study will be conducted in accordance with the Standard ISO 14155 and other legal requirements.
Study Objectives:	The primary objective is to evaluate the safety, performance and durability of the TIES® system to 12 months. Quality of Life (QoL) in subjects implanted with TIES® device will also be assessed as a secondary objective.
Study Treatment:	Subjects who are eligible for enrolment and can tolerate surgery will undergo a conventional ileostomy procedure under general anaesthesia. and the TIES® Port is implanted transcutaneous to form part of the stoma. Revision of the implant procedure, implantation of a second implant, or explantation is allowed based on investigator´s assessment.
Performance Evaluation	Performance evaluation is based on subject´s assessment of performance as recorded on the 3-day preceding each scheduled follow-up at 16, 24, 36 and 52 weeks after operation. Performance evaluation applies only among subjects with the TIES® Port *in situ.*

	Among subjects with the TIES® Port *in situ,* performance will be assessed according to (a) the proportion of subjects who use the TIES® Lid for continence control; (b) the proportion of subjects experiencing visible leakages around the implant; and (c) subject´s assessment on the ease of use of the TIES® Solution. Primary endpoint is absence of visible leakage or fecal staining of clothing at 24 weeks after implantation of the TIES® Port. The success criterion at 24 weeks requires at least 70% of subjects with the TIES® Port *in situ* having no visible leakage or staining of clothing adjacent to the implant between consecutive episodes of using the lid for continence control. Spillage that might occur at opening of the lid is not regarded as leakage. Secondary endpoints are • Absence of visible leakage or fecal staining of clothing at 16, 36 and 52 weeks. • Proportion of implanted subjects using the TIES® Lid for continence control at 16, 24, 36 and 52 weeks. • Subject´s assessment on the ease of use of the TIES® Lid using a visual analog scale 16, 24, 36 and 52 weeks after implantation. • Subject´s preference for the TIES® solution assessed at 52 weeks. The subject´s assessment on the ease of use of the TIES® Lid will provide feedback to the manufacturer regarding future refinements of the TIES® solution. Information will be collected in the diary to understand patient´s needs as described in section 10.
Durability Evaluation	Durability of use is evaluated by the cumulative proportion of subjects with the TIES® Port *in situ* at each of the following timepoints of 8,16, 24, 36 and 52 weeks. These are secondary endpoints. Durability will be computed by lifetable methods as the complement of the cumulative proportion of subjects in whom the TIES® Port has been removed or has spontaneously explanted, with subjects censored if they withdraw from the study with the device *in situ*, have insufficient follow-up time, or the device is removed for reasons unrelated to device performance.
Safety Evaluation	Safety outcome measures are secondary endpoints and will be analysed as proportion of all implanted subjects using descriptive statistics. Safety information will be collected during the following intervals: during hospitalisation, interval from discharge to 4-weeks visit, interval after the 4-weeks visit including 8-weeks visit, interval after the 8-weeks visit including 16-weeks visit, interval after the 16-weeks visit including 24-weeks visit, interval after the 24-weeks visit including 36-weeks visit, and interval after the 36-weeks visit including 52-weeks visit. Secondary endpoints are: • Proportion of implanted subjects with treatment emergent adverse events. Treatment emergent adverse events are defined as events with onset during or after the implantation

	procedure. • Proportion of implanted subjects with peristomal skin lesions will be evaluated using a validated 5-point scale by assessing signs of erythema, erosion, or papular lesions. • Proportion of implanted subjects with device-related adverse event. • Proportion of implanted subjects with device displacement, device revision or device replacement. Photographs of the stoma are to be taken to document the ingrowth into the TIES® Port, surrounding peristomal skin and position of the implant at 4, 8, 16, 24, 36 and 52 weeks after implantation.
Quality of Life Evaluation	Impact on quality of life will be evaluated by using two validated instruments EQ-5D-5L Quality of Life (QoL) questionnaire and Montreux Quality of Life questionnaire. Secondary endpoints are: Change in quality of life from baseline at 8, 16, 24, 36 and 52 weeks post implantation will be assessed among subjects with the device *in situ*.
Participating Sites:	Up to 25 sites will be enrolling in up to 6 countries in Europe and Asia.
Study Population and Sample Size:	A minimum of 200 patients will be enrolled. These patients have an indication for a permanent ileostomy, e.g., ulcerative colitis, familial adenomatous polyposis coli, or other diseases requiring elective colectomy; or patients with a medical need for an alternative to an existing conventional ileostomy or continent ileostomy or pelvic pouch.
Inclusion Criteria:	Subjects will be included if the following criteria are met: 1) Subject has ulcerative colitis, familial adenomatous polyposis coli or other diseases for whom a permanent ileostomy is indicated; or the subject has a medical need for an alternative to an existing conventional end-ileostomy, continent ileostomy or pelvic pouch; and 2) Patient is a male ≥18 years of age or female ≥18 years of age (See exclusion criterion 4 regarding female with childbearing potential); and 3) Signed written informed consent has been obtained prior to any study- related procedure.
Exclusion Criteria:	Subjects will be excluded if any one of the following conditions exists: 1) Concurrent gastrointestinal fistula, parastomal or incisional hernia, or a history of recurrent gastrointestinal fistula, recurrent parastomal hernia(s), and/or recurrent incisional hernia(s). 2) Patients with undetermined colitis.

	3) Patients with Crohn´s disease 4) Females who are of childbearing potential and do not wish to use birth control measures for the duration of the study 5) Patients receiving immunosuppressives, oncologic treatment or anticoagulants. 6) Any clinically significant, abnormal, baseline laboratory result which in the opinion of the surgeon, affects the patient's suitability for the study or puts the patient at risk if he/she undergoes surgery 7) Severe illness which, in the opinion of the surgeon may put the patient at risk when participating in the study or may affect the patient's ability to complete the study visits 8) Condition associated with the risk of poor protocol compliance, e.g. alcoholism and/or drug abuse, dementia, self-destructive personality disorder 9) Subjects with BMI ≤ 17 kg/m^2 or BMI ≥ 33 kg/m^2 10) Participate in other clinical studies that could interfere with the result in the ongoing study
Estimated Timelines	Estimated duration for enrolment: 48 months Duration of participation for each subject: 12 months Total study duration: 5 years
Clinical Study Organization:	Sponsor: OstomyCure AS Gaustadalléen 21 0349 Oslo, NORWAY
	Monitor : Devicia AB Argongatan 2C 431 53 Mölndal Sweden
	A Data Safety Monitoring Board will be appointed to review interim study results as discussed in section 9. A dermatologist will provide independent review of photographs of the stoma for peristomal skin lesions as required.

CLINICAL INVESTIGATION PLAN

Schedule of Assessments / Flow Chart:

Parameter/ Examination	*Screening*	*Baseline* [a]	*Procedure (day 0)*	*Post OP (Daily follow up* [c]*)*	*Discharge*	*Visit 1 at 4 Weeks (+/- 7d)*	*Visit 2 at 8 weeks*[e] *(+/- 7d)*	*Visit 3 at 16 weeks (+/- 7d)*	*Visit 4 at 24 weeks (+/- 14 d)*	*Visit 5 at 36 weeks (+/- 14 d)*	*Visit 6 at 52 weeks (+/- 14 d)*
Informed Consent		X									
Medical history	X	X									
Inclusion/Exclusion criteria	X	X									
Physical Examination[f]	X	X		X	X	X	X	X	X	X	X
Dipstick urine-analysis		X									
ECG		X									
Pregnancy test [b]		X									
Hematology and Chemistry		X									
Review and instruct on care of the stoma				X	X	X	X	X	X	X	X
Removal of Turnbull Adaptor[d]						X					
Start to use TIES® Lid							X				
Adverse Events (AE)			X	X	X	X	X	X	X	X	X
Safety evaluation			X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X
Ingrowth assessment						X	X	X	X	X	X
Photographs[g] of implant, stoma and adjacent skin			X		X	X	X	X	X	X	X
QOL questionnaires		X					X	X	X	X	X
Performance Questionnaire (Diary covering one 72-hours period)								X	X	X	X
Subject´s preference questionaire											X

[a] The patient will be considered as enrolled only when the consent will have been signed. All the examinations performed before the enrolment are done according to routine practice at the hospital where the study takes place. The baseline assessment should be performed not earlier than 12 weeks before the procedure.
[b] Pregnancy test will be performed in woman of childbearing potential.
[c] A follow up will be performed every day after the procedure prior to discharge from hospital.
[d] Removal of Turnbull system will be performed at 4 weeks (+/- 7 days) only if it has not already detached by itself.
[e] The patient will continue to permanently use stoma bags until visit at 8 weeks for review of suitability to start using the TIES®Lid. If trimming of ileum is required, postpone use of TIES® Lid by about a week for healing.
[f] Physical examination also includes weight measurement
[g] At least 4 views of the stoma should be taken: horizontal, vertical frontal, verical right and vertical left. Additional views may be required if skin lesions or device displacement develop.

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List of Abbreviations

Term	Definition
AE	Adverse event
ADE	Adverse Device Effect
BP	Blood Pressure
CA	Competent Authority
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Clinical Research Organization
CV	Curriculum Vitae
DCF	Data Clarification Form
EC	Ethics Committee
EDC	Electronic Data Capture System
FIH	First-in-Human
GCP	Good Clinical Practice
HR	Heart Rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
MPA	Medical Product Agency
NA	Not Applicable / Not Available
PMS	Post Market Study
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
SAE	Serious Adverse Event
SDV	Source Data Verification
TIES®	Transcutaneous Implant Evacuation System

Glossary

TIES® System	TIES® Port, Diathermy Leveller, Dummy (Sizer), Turnbull Adaptor, Stabiliser, Lid and Emptying Pouch
TIES® Surgical Aids	TIES® Diathermy Leveller, Dummy (Sizer) and Turnbull Adaptor (a sub-set of TIES® System used by the surgeon)
TIES® Port	TIES® Port is a titanium implant that is implanted transcutaneously to become part of the stoma. The TIES® Lid is put on the TIES® Port.

1. INTRODUCTION

The Transcutaneous Implant Evacuation System (TIES®) consists of an implantable TIES® Port and several aids that enables continence control for patients who would otherwise need to wear an ileostomy bag continuously following conventional ileostomy surgery. See section 2 on intended use and a description of the system.

1.1. Medical need for ileostomy and burden for patients

In some patients suffering from ulcerative colitis, familial polyposis and large bowel cancer, medical treatment alone is not sufficient and surgery is required for partial or total removal of the affected organ with construction of an ileostomy.

Three major types of ileostomies may be made based on individual needs as illustrated in Figure 1. They are (1) pelvic pouch or ileo-anal pouch where the colon is removed and a part of the ileum is used to form a pouch which connects to the rectum; (2) a procedure called continent ileostomy ad m. Kock; and (3) conventional ileostomy for patients unsuitable of (1) and (2), or failed ileo-anal pouch or continent ileostomy.

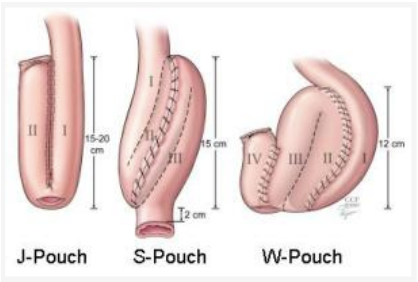
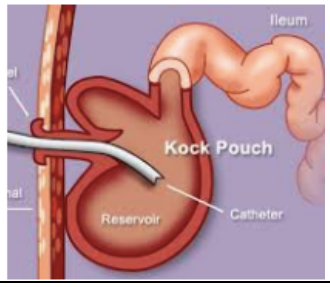
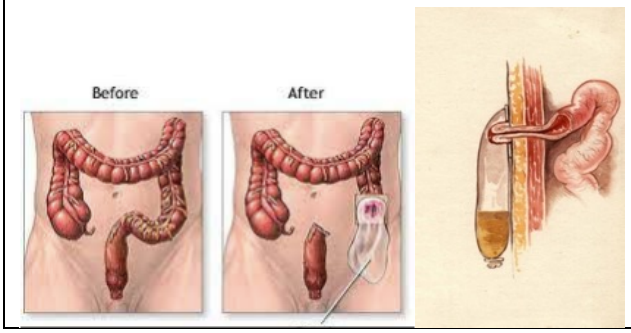
	Ileo-anal pouch (J, S or W variants)
	continent ileostomy (requiring drainage via catheter)
	conventional ileostomy (drainage into a stoma bag)

Figure 1 Illustrations of 3 major types of ileostomies

Each of these three procedures are associated with complications and failure rates (Refer to Investigator´s Brochure). Known complications associated with conventional ileostomy include poor stoma siting, high output, ischemia, retraction, parastomal hernia and prolapse; with skin irritation, a common problem affecting at least 30% of patients due to exposure to intestinal contents or use of the stoma bags.

Serious complications requiring reoperations can also occur, as can minor problems that will subject the patient to daily and nightly discomfort.

1.2. Transcutaneous Implant Evacuation System (TIES®) as an add-on to the stoma of conventional ileostomy to enable continence control

Patients with conventional ileostomy have to wear a stoma bag attached to the abdomen for collection of faeces continuously. Despite the availability of a large number of light weight, hygienic and discrete bags, many patients suffer from complications such as skin problems, leakage and odour, and for some the mere change of body image results in social isolation. The titanium Port of the Transcutaneous Implant Evacuation System (TIES®), which is the subject of this study, is placed onto the surgical opening or stoma after intestinal segment resection and provides a permanent patient-controlled continent stoma for emptying of intestinal wastes and reduces/ obviates the need of using a stoma bag. It is hoped that by eliminating seepage, odour, noise, and the need for permanently wearing stoma appliance, quality of life will be improved.

1.3. Study rationale

The TIES® System has been studied in two studies (C01 and C02) involving a total of 11 patients and 13 implantation procedures. This study is planned to collect more data on patients using the TIES® System for continence control. This study will evaluate safety, performance, durability and impact on quality of life in this patient population.

While the two completed studies gave assurance on the safety and reversibility of the procedure, most of the enrolled subjects had complicated baseline medical histories including failed pelvic pouch, failed continent ileostomy or experienced complications associated with previous ileostomy such as parastomal hernia or granulomatous overgrowth. The subject who achieved the best outcome for continence control using the TIES® Port in the C02 study was the one subject who had not undergone previous abdominal surgery.

In addition, based on learnings from the two previous studies, the eligibility criteria have been further refined in this study and clarification included in the protocol on post-implantation care and the adaptation period.

1.4. Pre-Clinical Testing

Development of the TIES® implant has been ongoing since 2004. Previous animal testing on pigs and dogs showed the growth of tissue into the implant (ref 30 Johansson ML et al). During these studies the method of implantation, implant design has gradually evolved and improved with documentation of safety and performance. (See Investigator´s Brochure)

1.5. Completed Clinical Studies

The implantation and implantation method has been modified gradually since the first clinical

study in 2009. Based on knowledge gained from the two studies, this has led to improvements in both the implant, patient selection and post-implantation care.

The two small pre-market studies on the use of the TIES® system in humans provided data on a total of 11 subjects who were implanted with TIES® Port. In retrospect many of the subjects had baseline surgical conditions that may have impacted on the final outcome from implantation of the Port. For example, some of the subjects had pre-existing incisional or parastomal hernia and the Port was explanted as part of the hernia repair procedure.

Implants remained in situ for longer than 6 months in ten subjects, longer than 12 months in five subjects and over 60 months in three subjects who are still requesting supply of TIES® Lid from the manufactuer. One subject developed an enterocutaneous fistula and this subject also had a pelvic pouch removed at the same surgery for implantation of the Port, the possibility cannot be excluded that this surgery or the surgical staples left behind might have contributed to the formation of the fistula. No unanticipated serious device related adverse events were reported. In those subjects who were either explanted or implanted with a second Port, the Port could be explanted without any difficulties and conversion to a conventional ileostomy could be performed without complications. This gives assurances for safety before proceeding with implantation in a larger group of patients, including those undergoing ileostomy for the first time. (See Investigator´s Brochure)

2. TRANSCUTANEOUS IMPLANT EVACUATION SYSTEM

2.1. Overview of the TIES system

2.1.1. Overview of the Transcutaneous Implant Evacuation System (TIES®)

The Transcutaneous Implant Evacuation System (TIES®) is a complete method for constructing a stoma after intestinal segment resection. The TIES® system represents a concept for continent stoma creation in gastroenterological surgery. The system prevents seepage, and reduces or even may eliminate the need for wearing an external appliance (e.g. pouch/bag) on the abdomen after removal of the large intestine for collection of intestinal contents.

The TIES® system is composed of the TIES® Port, TIES® Surgical Aids, TIES® Stabiliser and TIES® Lid and Emptying Pouch. Only the TIES® Port is implanted. The three TIES® Surgical Aids are tools used at the surgical procedure to optimise the surgical procedure. They comprise of Diathermy Leveller to guide optimal depth for the Port, Dummy (Sizer) to verify suitable fit and the TIES® Turnbull Adaptor clipped onto the cylinder top of the Port for use during the ingrowth period. The TIES® Stabiliser is placed under the TIES® Turnbull Adaptor and is used to secure the port above the skin during healing. The TIES® Turnbull Adaptor is removed when the intestine has grown enough into the implant if it has not already detached by itself. The TIES® Stabiliser is left longer until the TIES® Lid can be used from about 2 months after the implant procedure.

An overview of the system and the products is included below in Figure 2.

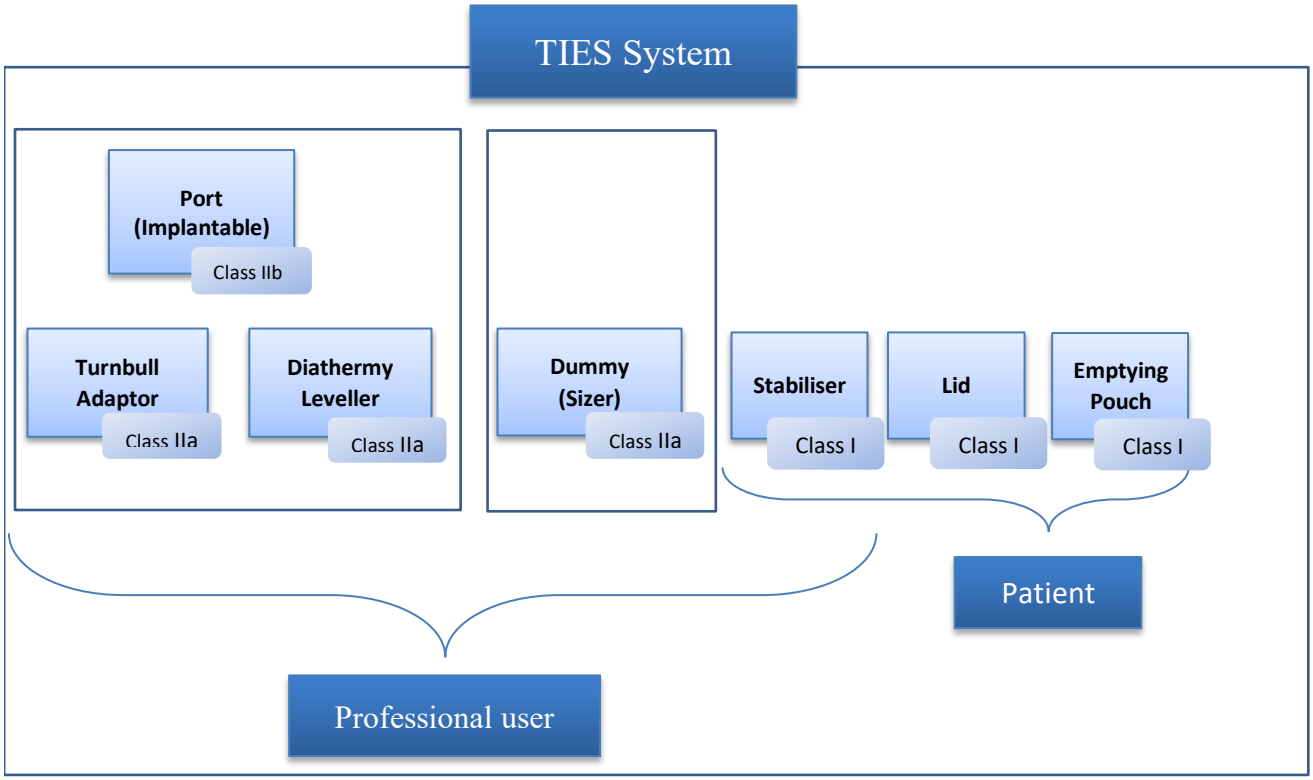
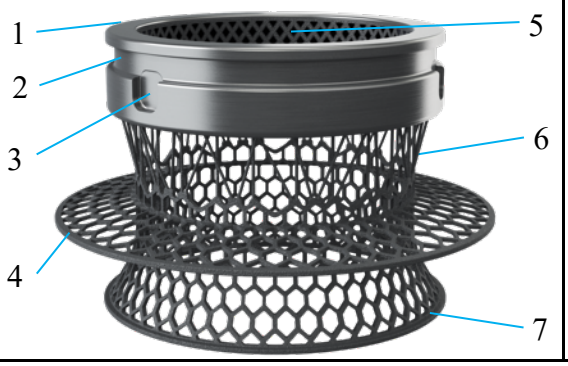


Figure 2 TIES system overview

2.1.2. Description of the components of the TIES® system

TIES® Port (Figure 3) is a titanium implant that is implanted transcutaneously and anchored in the subcutaneous fat and penetrates the skin. The ileum is attached through the implant to create a stoma. The implant is manufactured by laser melting of medical grade titanium powder. The Port comprises five functional sections: Cylinder Top, Upper Ingrowth Zone, Subdermal Ingrowth Zone, Anchor & Cylindrical Scaffolding and two technical features: Lid Groove and Turnbull Adaptor Notch as shown in Figure 3 below. The Anchor is an integrated disc that secures the implant in the subcutaneous fatty tissue. TIES® Port is supplied sterile in a single use sterile bag and must be implanted using sterile technique.



TIES® Port

1. Cylinder Top
2. Lid Groove
3. Turnbull Adaptor Notch
4. Anchor
5. Upper Ingrowth Zone
6. Subdermal Ingrowth Zone
7. Cylindrical Scaffolding

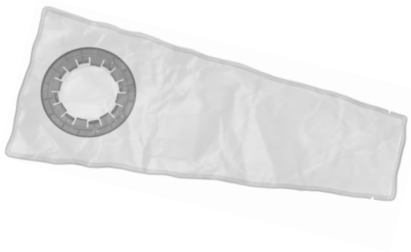
Figure 3 TIES Port

TIES® Surgical Aids consist of three simple aids that optimize the surgical procedure for the TIES® Port.

TIES® Diathermy Leveller (Figure 4) is an optional support plate against the skin that is snap-locked onto the diathermy electrode when making a circular incision for the Anchor in the sub-cutis. This is to ensure that the incision is at the optimum depth (8 mm) and is fully level relative to the skin. The Diathermy Leveller also contains a fixture that ensures that the diathermy electrode point can be bent at approximately 90° at the correct place. It is supplied sterile in a single use sterile bag and must be used using sterile technique.	 Figure 4 Diathermy Leveller
TIES® Dummy, or Sizer, (Figure 5) is used to verify that the ileum will fit well with the Port. It is supplied sterile in a single use sterile bag and must be used using sterile technique.	 Figure 5 TIES Dummy (Sizer)
TIES® Turnbull Adaptor (TA) (Figure 6) is an applicator that is positioned (clipped) on to the Cylinder Top of the Port. The TA is used to flip the end part of the intestine over its edge and suture the intestine to the outer circumference of the TA. TIES® Turnbull Adaptor is supplied sterile in a single use sterile bag and must be used using sterile technique.	 Figure 6 Turnbull Adaptor

TIES® aids to be used after surgery

TIES® Stabiliser (Figure 7) is used to secure the Port and to provide support above skin level during the in-growth period. It consists of a pair of Spacers used together with a Locking Ring as shown in fig 5. It is affixed to the Port after surgery is completed, fitting into the Lid Groove on the Cylinder Top of the Port. TIES® Stabiliser is supplied clean and disinfected but not sterile. It is handled in a non-sterile environment and is re-usable. It can be rinsed in tap water but will withstand household detergents. It can also be soaked in 70 % alcohol. The TIES® Stabiliser should be replaced every week.	 Figure 7 TIES Stabiliser

TIES® Lid (Figure 8) is a removable cap attached to TIES® Port. It is used to achieve a continent stoma after the ileum has grown into the implant and healed completely. The Lid has an integrated emptying hole that can be opened to empty the stoma without removing the Lid. TIES® Lid is re-usable and can be cleaned in the same way as the Stabiliser. Replace the Lid every week.	 Figure 8 TIES Lid
TIES Emptying Pouch (figure 9) is a dedicated accessory to the Lid, used when emptying the intestinal content. The pouch is placed over the Lid, with the connector fitting into the groove around the base of the Lid. The pouch has a tear-off base for simple conversion into an open-ended sleeve, allowing for emptying either into the pouch or directly into the toilet. The Emptying Pouch is intended for single use.	 Figure 9 TIES Emptying Pouch

Refer to the TIES® Surgical Procedure Manual and the TIES® User Care Manual in the appendix for further explanations and instructions (See Appendices).

2.2. Intended use

The objective for TIES® is to provide a continent, sanitary, odourless system to be used in various patient groups investigated in previous studies:

- Patients with diseases such as ulcerative colitis, familial adenomatous polyposis coli, multiple colonic cancers or other diseases requiring elective colectomy followed by a permanent ileostomy, ileo rectal anastomosis or ileal pouch-anal anastomosis.
- Patients with a failing conventional ileostomy, continent ileostomy, ileo-rectal anastomosis or ileal pouch-anal anastomosis.

Patients with Crohn's disease will not be enrolled in the trial.

The implant or TIES® Port is used to construct a stoma by implantation in the abdominal wall, penetrating the skin, and is anchored in the dermal and subcutaneous tissues. The ileum outlet is passed through the implant. The internal mesh structure in the TIES® Port implant facilitates a biological attachment of the bowel segment to the implant. The Turnbull Adaptor is clipped on the cylinder top of the TIES® Port. It is used during the first weeks to provide optimum in-growth conditions by securing the ileum above the TIES® Port. The Stabilizer is positioned around the implant in order to secure the implant and provides support above skin level during the in-growth period.

During the first weeks, patients will have to use standard stoma bags. Below is a drawing (Figure 10) of a cross section of abdominal wall displaying the TIES® Port connected to a conventional ileostomy stoma.

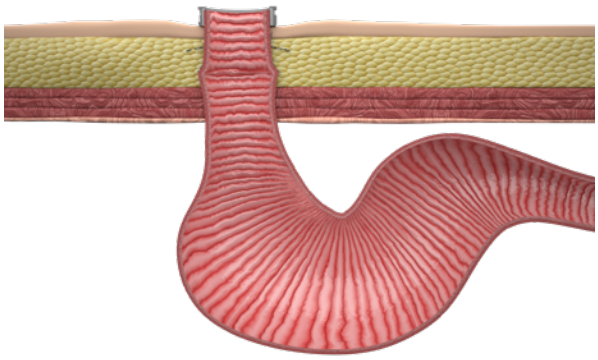


Figure 10 Cross-section showing the ileum connected to the TIES Port (no Lid attached).

After about four weeks the intestine has grown enough into the implant for the Turnbull Adaptor to be removed, if the Turnbull Adaptor has not already detached by itself from the stoma.

The part of the intestine protruding outside the implant has now started to wizen and, if necessary, is trimmed away by the surgeon in a simple procedure if required and the intestine will now reside permanently just at the top of the implant.

Once the implant is healed and fully integrated into the tissue, the top of the implant can be closed with a TIES® Lid. The TIES® Lid has an integrated emptying hole which can easily be opened and closed. Together with a TIES Emptying Pouch, this allows for the system to be emptiedin a soil-free procedure.

Figure 11 The ileostomy is being emptied with an irrigation sleeve.

2.3. Manufacturing

The manufacturing of the Port is subcontracted by OstomyCure AS to 3DSystems, an ISO13485 approved medical device subcontractor. The TIES® Port is sterilized with steam sterilisation by autoclaving. Please refer to the Investigators Brochure for more detailed manufacturing information of all system parts.

2.4. Training

The Sponsor is responsible for providing site personnel with the information and training they need to conduct the study properly. Study-specific training and education is required for all site staff with roles in this trial. The Sponsor is responsible for maintaining documentation of attendance at each of the training sessions provided.

The Sponsor personnel will provide training and technical support on the TIES® System and procedure to the Investigator and other health care personnel as needed before and during procedure and testing required by the protocol. In addition, the Sponsor personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy on the performance of the procedure

3. STUDY DESIGN

This is a multi-center, open study that evaluates the safety, performance and durability of the TIES® transcutaneous titanium implant to 12-months post implantation.

This study will be conducted in accordance with the Standard ISO 14155 and other legal requirements.

3.1. Rationale for the Study Design

As discussed previously, there are currently 3 different surgical approaches for patients requiring a permanent ileostomy, namely pelvic pouch, continent ileostomy and conventional ileostomy. The choice of the procedure is based on individual needs. The TIES® system offers a unique function in that the TIES® Port allows the use of a TIES® Lid to control intestinal emptying as required, as an alternative to using stoma bag to collect waste continuously from conventional ileostomy. It is also indicated as a treatment for patients with failed pelvic pouch or continent ileostomy. A single arm study is appropriate in this context.

The TIES® Port is implanted transcutaneously so that it becomes part of the stoma to a conventional ileostomy. A pre-requisite for success is to engage only surgeons who are skilled in performing ileostomy.

The study population includes patients with ulcerative colitis, familial adenomatous polyposis coli, other diseases requiring elective colectomy with a permanent ileostomy, or patients requiring a permanent ileostomy; or patients with a medical need for an alternative to an existing conventional ileostomy, continent ileostomy or pelvic pouch.

Only limited conclusions on outcomes can be drawn from the two previous studies because most enrolled subjects were converted from pelvic pouch, continent ileostomy or had complications associated with previous conventional ileostomy. It is relevant to study more patients who have not undergone previous complicated abdominal surgeries. By enrolling 200 subjects, this gives an opportunity to enrol patients undergoing ileostomy for the first time without needing conversion from pelvic pouch, continent ileostomy or pre-existing ileostomy complicated by incisional or parastomal hernia.

The objective of the study is to collect data to evaluate the safety, performance, durability of the implant and impact on quality of life in a group of subjects needing a permanent ileostomy

(as described in the intended use). Acceptability of the implant to study subjects is part of performance evaluation. Because the subject will need to use a stoma bag in the initial healing phase, subject´s preference for the TIES® solution for continence control versus stoma bag can be evaluated in this single-arm study.

This protocol plans for five interim data analyses. The first two interim analysis are planned after collection of 8-week results from the first 5 and of 24-week results of the first 20 subjects respectively, to review all available study data and to assess if there is a need to modify the study protocol including adjusting the collection of outcome measurements for performance assessment. The third, fourth and fifth interim analyses will be conducted when 50, 100 and 150 subjects, respectively, have completed 24 weeks follow-up in order to assess the primary and secondary 24-week safety and performance endpoints, make a preliminary assessment of the types of patient with high device acceptability, and consider whether some of the secondary study instruments (e.g. Quality of Life Questionnaires) can be dropped for the remaining patients to simplify follow-up and reduce burden on patients and clinical teams.

The final analysis will be carried out after the last subject has completed the 52-week assessment.

3.2. Participating Sites and Study Population

Up to 25 sites will be enrolling in up to 6 countries in Europe and Asia. A minimum of 200 patients will be enrolled, with a history of ulcerative colitis, familial adenomatous polyposis coli, other diseases requiring elective colectomy with a permanent ileostomy, or patients with a failing conventional or continent ileostomy or pelvic pouch. This study population is representative of the devices intended target population. These patients will be followed for 12 months after the implantation procedure. Enrolment is expected to take approximately 48 months due to Covid-19

4. STUDY OBJECTIVE AND ENDPOINTS

The primary objective is to evaluate the safety, performance and durability of the TIES® Port to 52 weeks in subjects after implantation. The secondary objective is to evaluate Quality of Life (QoL) in subjects implanted with the TIES® Port.

4.1. Performance Evaluation

Performance evaluation is based on subject´s assessment of performance as recorded on the 3-day diary preceding each scheduled follow-up at 16, 24, 36 and 52 weeks after operation. Performance evaluation applies only among subjects with the TIES® Port *in situ.*

Among subjects with the TIES® Port *in situ,* performance will be assessed according to (a) the proportion of subjects who use the TIES® Lid for continence control; (b) the proportion of subjects experiencing visible leakages around the implant; and (c) subject´s assessment on the ease of use of the TIES® Solution.

Primary endpoint is absence of visible leakage or fecal staining of clothing at 24 weeks after implantation of the TIES® Port.

The success criterion at 24 weeks requires at least 70% of subjects with the TIES® Port *in situ* having no visible leakage or staining of clothing adjacent to the implant between consecutive episodes of using the lid for continence control. Spillage that might occur at opening of the lid is not regarded as leakage.

Secondary endpoints are

- Absence of visible leakage or fecal staining of clothing at 16, 36 and 52 weeks.
- Proportion of implanted subjects using the TIES® Lid for continence control at 16, 24, 36 and 52 weeks.
- Subject´s assessment on the ease of use of the TIES® Lid using a visual analog scale 16, 24, 36 and 52 weeks after implantation.
- Subject´s preference for the TIES® solution assessed at 52 weeks.

The subject´s assessment on the ease of use of the TIES® Lid will provide feedback to the manufacturer regarding future refinements of the TIES® solution. Information will be collected in the diary to understand patient´s needs as described in section 10.

4.2. Durability Evaluation

Durability of use is evaluated by the cumulative proportion of subjects with the TIES® Port *in situ* at each of the following timepoints of 8,16, 24, 36 and 52 weeks. These are secondary endpoints.

Durability will be computed by lifetable methods as the complement of the cumulative proportion of subjects in whom the TIES® Port has been removed or has spontaneously explanted, with subjects censored if they withdraw from the study with the device *in situ*, have insufficient follow-up time, or the device is removed for reasons unrelated to device performance.

4.3. Safety Evaluation

Safety outcome measures are secondary endpoints and will be analysed as proportion of all implanted subjects using descriptive statistics. Safety information will be collected during the following intervals: during hospitalisation, interval from discharge to 4-weeks visit, interval after the 4-weeks visit including 8-weeks visit, interval after the 8-weeks visit including 16-weeks visit, interval after the 16-weeks visit including 24-weeks visit, interval after the 24-weeks visit including 36-weeks visit, and interval after the 36-weeks visit including 52-weeks visit.

Secondary endpoints are:

- Proportion of implanted subjects with treatment emergent adverse events. Treatment emergent adverse events are defined as events with onset during or after the implantation procedure.
- Proportion of implanted subjects with peristomal skin lesions will be evaluated using a validated 5-point scale by assessing signs of erythema, erosion, or papular lesions.
- Proportion of implanted subjects with device-related adverse event.
- Proportion of implanted subjects with device displacement, device revision or device replacement.

Photographs of the stoma are to be taken to document the ingrowth into the TIES® Port, surrounding peristomal skin and position of the implant at 4, 8, 16, 24, 36 and 52 weeks after implantation. At least 4 views are to be taken: horizontal, vertical frontal, vertical right and vertical left. Additional views may be required if skin lesions or device displacement develop.

4.4. Quality of Life Evaluation

Impact on quality of life will be evaluated by using two validated instruments EQ-5D-5L Quality of Life (QoL) questionnaire and Montreux Quality of Life questionnaire.

Secondary endpoints are:

Change in quality of life from baseline at 8, 16, 24, 36 and 52 weeks post implantation will be assessed among subjects with the device *in situ*.

5. SUBJECT SELECTION

A minimum of 200 patients will be enrolled. These patients have an indication for a permanent ileostomy, e.g., ulcerative colitis, familial adenomatous polyposis coli, or other diseases requiring elective colectomy; or patients with a medical need for an alternative to an existing conventional ileostomy or continent ileostomy or pelvic pouch.

5.1. Inclusion Criteria (IC)

Subjects will be included if the following criteria are met:

1) Subject has ulcerative colitis, familial adenomatous polyposis coli or other diseases for whom a permanent ileostomy is indicated; or the subject has a medical need for an alternative to an existing conventional end-ileostomy, continent ileostomy or pelvic pouch; and
2) Patient is a male ≥18 years of age or female ≥18 years of age (note exclusion criterion 4 regarding female with childbearing potential); and
3) Signed written informed consent has been obtained prior to any study- related procedure.

5.2. Exclusion Criteria (EC)

Subject will be excluded if any one of the following conditions exists:

1) Concurrent gastrointestinal fistula, parastomal or incisional hernia, or a history of recurrent gastrointestinal fistula, recurrent parastomal hernia(s), and/or recurrent incisional hernia(s).
2) Patients with undetermined colitis.
3) Patients with Crohn´s disease
4) Females who are of childbearing potential and do not wish to use birth control measures for the duration of the study
5) Patients receiving immunosuppressives, oncologic treatment or anticoagulants.
6) Any clinically significant, abnormal, baseline laboratory result which in the opinion of the surgeon, affects the patient's suitability for the study or puts the patient at risk if he/she undergoes surgery
7) Severe illness which, in the opinion of the surgeon may put the patient at risk when participating in the study or may affect the patient's ability to complete the study visits
8) Condition associated with the risk of poor protocol compliance, e.g. alcoholism and/or drug abuse, dementia, self-destructive personality disorder
9) Subjects who are underweight or obese with BMI ≤ 17 kg/m^2 or BMI ≥ 33 kg/m^2
10) Participate in other clinical studies that could interfere with the result in the ongoing study

5.3. Subject Accountability

5.3.1. Enrolled subjects

The point of enrolment is the time at which, following recruitment, a subject signs and dates the informed consent to agree to participate in the clinical investigation. Subject for whom consent was not obtained prior to participation in the study will not be considered enrolled. No data from subject who has not provided signed informed consent will be included in any analysis.

5.3.2. Screen failures

A screen failure is a subject who does not meet all eligibility criteria and therefore will not be enrolled into the study and no informed consent form will be signed. A screening log will contain information on all subjects screened identified by the Subject Identification number. For screened failures, the eligibility criterion/ criteria that are not met will be recorded.

5.3.3. Treated Subjects

An enrolled subject who meets all eligibility criteria, and has been implanted with the TIES® Port will be followed in accordance with the protocol requirements.

Any enrolled subject in whom the TIES® Port implantation procedure is attempted but not successfully implanted will be followed for 6 months after the implantation procedure and then exit the study.

5.3.4. Withdrawal

Early termination of study participation will be documented for patients that have signed an informed consent form and who exited for any of the following reasons:

- Subject for whom the implantation procedure has been attempted but cannot completed, for example, due to technical reasons. (These subjects will be followed for six months.)
- Subject who are explanted. (These subjects will be followed for six months.)
- Subject no longer wishes to continue with the study follow-up. No further follow up applies.
- Investigator believes it is the best medical interest of the subject to discontinue study participation due to safety reasons. (These subjects will be followed until study procedure related adverse events have resolved.)
- Death of the subject.

No additional subjects will be recruited to compensate for subjects who withdraw or are withdrawn from the study.

6. STUDY PROCEDURES AND ASSESSMENTS

6.1. Subject Identification

Each subject will be given a Subject Identification Number for tracking purposes from screening, enrolment and throughout study participation. Use of a Subject Identification

Number is intended to assure confidentiality for subjects. Subject numbers will be issued chronologically by the EDC following signed informed consent.

6.2. Screening

At the screening visit, each potential subject will be allocated a Subject Identification Number for tracking purposes and it is intended to assure confidentiality for subjects.
A full medical history including concomitant medications and physical examination will be performed in accordance with standard of care. Subjects will be assessed according to the eligibility criteria. They will not undergo any tests or procedures that are study specific and are not standard clinical practice.

The screening visit may be combined with the baseline visit.

Subjects who do not meet the eligibility criteria are regarded as screen failures. A screening log should be kept and will be a record on all subjects screened identified by the Subject Identification number. For screened failures, the eligibility criterion/ criteria that are not met should be recorded.

6.3. Enrolment

Only subjects who meet the eligibility criteria will be approached to participate in the study. Subjects are enrolled into the study after providing signed informed consent to participate in the study.

6.4. Informed Consent Process

The Informed Consent Form can only be used after the clinical investigation has been fully approved by the Competent Authority and Institution's Ethics Committee (EC). The Sponsor or their CRO representative should be informed on the approved Informed Consent form before it is implemented in the study.

When the Investigator has determined the eligibility of a specific subject to enter this study, the Investigator will provide an informed consent form to the subject. The Investigator or designee will discuss and explain the clinical investigation with the subject as following:

- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The Investigator will obtain a signed informed consent form from the subject before performing the TIES® implant procedure or any protocol-specific tests. The Investigator will provide subjects with a copy of their signed informed consent form. The Investigator will provide new information to new and existing subjects.

The Investigator will maintain a copy of the EC-approved Informed Consent Form along with a copy of each subject's signed Informed Consent Form in a designated study file.

6.5. Baseline Visit

The baseline visit may be combined with the screening visit. A full medical history including concomitant medications and physical examination will be performed in accordance with standard of care. Subjects will be assessed according to the eligibility criteria. They will not undergo any tests or procedures that are study specific and are not standard clinical practice until informed consent has been provided.

Each subject will be given a Subject Identification Number for tracking purposes and it is intended to assure confidentiality for subjects.
After confirming that all the inclusion and exclusion criteria are met, Informed consent will be discussed.

The following examinations are regarded as part of pre-operative assessment and the results are to be recorded in the medical case notes in accordance with requirements of the institution where the surgical procedure will be performed:

- Demographics, medical history and concomitant medications
- Physical examination
- Pregnancy test in woman of childbearing potential
- Pre-operative ECG
- Hematology and Chemistry
- Dipstick urine analysis
- Assessment by the stoma/research nurse and siting of stoma if required

The following information will be collected in the case report forms (CRFs):

- Demographics
- Medical history including indications for ileostomy and previous surgeries
- Concomitant medications
- Document in CRFs if the following procedures have been performed and any abnormal findings: physical examination, pre-operative ECG, hematology and chemistry tests, dipstick urine analysis
- Record if pregnancy test has been performed and the result
- Record if assessment by the stoma/research nurse has been performed and any abnormal findings
- Quality of Life (QoL) Questionnaire/s

6.6. TIES® Port Implantation Procedure

Detailed instructions on implanting the TIES® Port and on connecting the distal ileum to the TIES® Port can be found in the Surgical Procedure Manual (see Appendix).

6.6.1. Subject Preparation

The subject will be prepared for the implantation surgery, per the Surgical Procedure Manual (see Appendix), and per the hospital's standard for ileostomy surgeries including siting of the stoma prior to surgery.

6.6.2. Implantation Procedure

Performance on the implantation procedure will be captured as well as any Adverse Events (AE) that occurred during the procedure. A list of the TIES®surgical aids used should be recorded. Any changes in the doses or discontinuation of concomitant medications will also be documented.

6.6.3. Post operation care

The patient will be followed up daily before their discharge for the stoma/device and general health condition, as follows:

- Adverse Event and safety evaluation
- Changes in concomitant medications
- Cleaning procedure according to patient's needs (the same as used in conventional ileostomies) will be performed; the stabilizer can be left in place during cleaning.

6.6.4. Bail Out Procedure (if applicable)

All bailout procedures, that is, conversion to a conventional ileostomy, and all adverse events associated with the procedure should be documented.

Refer, also, to section 6.16.2 on explant procedure.

6.7. Hospital Discharge

Before discharge from the hospital, the following study assessments/activities will be performed:

- Examination of the subject and the stoma
- Photographs of the stoma and adjacent skin
- Adverse Event evaluation
- Record any changes in concomitant medications
- Cleaning procedure, according to schedule will be performed;
- Instructions provided to the patients on care of the stoma.
    - A patient´s guide on care of the implant and use of the TIES® Lid for the first 16 weeks after implantation is included in the Appendix.

6.8. Turnbull Adaptor Removal

The Turnbull Adaptor will be removed at 4 weeks (+/- 7 days) if it has not already detached from the stoma. The patient will continue to use a stoma bag for several weeks after that time until the stoma is sufficiently healed to allow introduction of the TIES® Lid and subsequent regular use of the TIES®Lid.

6.9. Follow-Up Visits

Follow-up visits for this study are planned at 4, 8, 16, 24, 36 and 52 weeks after the implantation procedure. They are named consecutively from Visit 1 to Visit 6. All visits are office visits except for Visit 5 at 36 weeks and Visit 6 at 52 weeks that can be conducted via video-conferencing if the subject is unable/unwilling to make the journey. The subject will be instructed to take photographs and forward these to the site. An office visit might still be carried out depending on the assessment during the video-conference.

Unscheduled office visits can be carried out if there is a medical need.

For subjects who require a second implant, the timing of the follow-up visits will commence after the new implantation procedure.

For subjects who require a revision of the implant, the timing of the follow-up visits may or may not need to be readjusted following the revision procedure, based on the assessment by the investigator.

Photographs showing the implant and peristomal skin will be taken to as study documentation at every follow-up visit as described below in section 6.12.

The following assessments/activities will be performed at follow-up visits.

6.9.1. Visit 1 at 4 weeks (+/- 7 days) at the office

- Physical examination including evaluation of ingrowth into the stoma
- Inspect healing around the stoma and implant
- Review and instruct on care of the stoma
- Removal of Turnbull Adaptor if it has not already detached from the stoma (see Surgical Procedure Manual, in Appendix)
- Adverse event and safety evaluation
- Concomitant medications review
- Photographs of the implant, stoma and adjacent skin

6.9.2. Visit 2 at 8 weeks (+/- 7 days) at the office

- Physical examination including evaluation of ingrowth into the stoma
- Evaluate if the healing around the implant is sufficient for start of TIES® Lid use
  - Trimming of excess intestinal tissue to about 5 mm above the top of the cylinder of the Port if required
  - If trimming is performed, postpone start of use of TIES® Lid by one week for healing
- Review and instruct on care of the stoma
- Adverse event and safety evaluation
- Concomitant medications review
- Photographs of the implant, stoma and adjacent skin
- Complete EQ-5d and Montreux Quality of Life Questionnaires
- Provide instructions on the 72-hour subject´s diary to be completed prior to the next visit

6.9.3. Visit 3 at 16 weeks (+/- 7 days) at the office

- Physical examination including evaluation of ingrowth into the stoma
- Review and instruct on care of the stoma
- Adverse event and safety evaluation
- Concomitant medications review
- Photographs of the implant, stoma and adjacent skin
- Review if the required 72-hour subject´s diary has been completed and provide the subject a new diary to complete prior to the next visit
- Review if the required EQ-5d and Montreux Quality of Life Questionnaires have been completed

6.9.4. Visit 4 at 24 weeks (+/- 14 days) at the office

- Physical examination including evaluation of ingrowth into the stoma

- Review and instruct on care of the stoma
- Adverse event and safety evaluation
- Concomitant medications review
- Photographs of the implant, stoma and adjacent skin
- Review if the required 72-hour subject´s diary has been completed and provide the subject a new diary to complete prior to the next visit
- Review if the required EQ-5d and Montreux Quality of Life Questionnaires have been completed

6.9.5. Visit 5 at 36 weeks (+/- 14 days) at the office or via video-conferencing

- Physical examination including evaluation of ingrowth into the stoma
- Review and instruct on care of the stoma
- Adverse event and safety evaluation
- Concomitant medications review
- Photographs of the implant, stoma and adjacent skin
- Review if the required 72-hour subject´s diary has been completed and provide the subject a new diary to complete prior to the next visit
- Review if the required EQ-5d and Montreux Quality of Life Questionnaires have been completed

6.9.6. Visit 6 at 52 weeks (+/- 14 days) at the office or via video-conferencing

- Physical examination including evaluation of ingrowth into the stoma
- Review and instruct on care of the stoma
- Adverse event and safety evaluation
- Concomitant medications review
- Photographs of the implant, stoma and adjacent skin
- Review if the required 72-hour subject´s diary has been completed and provide the subject a new diary to complete prior to the next visit
- Review if the required EQ-5d and Montreux Quality of Life Questionnaires have been completed
- Complete subject´s preference questionnaire

6.10. Unscheduled Visits

Subject may contact the investigator or the stoma/research nurse at any time outside of the scheduled follow-up visits. If there is a need for an unscheduled visit, for example, to evaluate adverse events, this should be documented in the case report forms.

6.11. Follow-up treatment after end of investigation

The investigation sponsor will provide explantation of the device during the clinical investigation if necessary (see Explantation procedure, below). At the end of the investigation, subjects have the right to choose whether to retain the device or to have the device removed. The same applies should the investigation be temporarily halted, or early terminated. The decision will be made in accordance with the investigator and based on

investigator judgement. If the subject keeps the device in place, the subject will be followed up by his/her general stoma team per standard stoma care and standard care for a non CE-marked device outside the investigation.

6.12. Photography of the stoma including the implant and peristomal skin

Photographs should be taken to show extent of ingrowth into the implant and around the implant at every visit and as needed if any complications develop. The photographs should include the peristomal skin, particularly if peristomal skin lesions are noted or suspected. The subject identification number, the view and the Visit number are to be included in the photographs.

The following views are required:

1. Horizontal view with the subject in the supine position:
    - "Horizontal View (HV)" – photograph of the implant and peristomal skin from above;
2. 3 Vertical views with the subject standing upright:
    - Vertical frontal view (FV) – photograph of the implant and peristomal skin taken from the front,
    - Vertical right view (RV)- photograph of the implant taken from the right, and,
    - Vertical left view (LV)– photograph of the implant taken from the left.

The photographs are to be uploaded into the electronic case report form system. Care should be taken so that the identity of the subject is not disclosed in the photographs. The files should be labelled by renaming the image file using the following convention study comprising of number_subject ID_photograph view_visit number, eg TIESIIIC03_9901_RV_4 weeks.
A printed copy of the photographs should be kept as part of medical records at the site and these should be labelled by the subject number, the view and the Visit number.

6.13. Quality of Life (QoL) Questionnaires

Quality of Life questionnaires will be provided to the subjects, with instructions on how and when the questionnaires should be completed at baseline and from Visit 2 onwards. The QoL questionnaires can be completed either prior to the visit or during the office visit. These questionnaires can be filled in on the internet or on paper. Those QoL questionnaires include:

- EQ-5d quality of Life Questionnaire
- Montreux Quality of Life Questionnaire (specific to stomas)

See Appendix for more details on the QoL questionnaires.

6.14. TIES® System Performance Evaluation Questionnaire – Subject´s diary

A TIES® System Performance Evaluation Questionnaire will be provided to the subjects in the form of a 72-hour diary, with instructions on how and when the questionnaire should be completed per the study visit schedule. See Appendix for more details.

6.15. Subject´s Preference Evaluation

A Subject´s preference questionnaire will be provided to the subjects to respond to at the last study visit at 52 weeks. Appendix for more details.

6.16. General Investigational Device Management

6.16.1. Device Accountability

A device accountability log for the TIES® Port and all appliances used shall be kept for this study. Lot numbers must be included in the accountability log. A copy of the completed accountability log will be kept on site for traceability for all subjects, including early terminations. Access to device is restricted to delegated staff in the investigation. Unused and expired devices will be returned to Sponsor at the end of the investigation.

6.16.2. Explant Procedure (if applicable)

If the TIES® Port must be removed, it can be done using standard surgical procedures.

Should there be a reason for explanting the implant and/or the surrounding tissue, it shall be removed in a manner that causes minimal damage to both the implant and the tissues. It is particularly important that implant surfaces and adjacent tissues are kept intact.

See the Surgical Procedure Manual (Appendix) for further detail.
Information on the explant procedure must be documented in source notes and captured in the Case Report Form on “Explant procedure”.
All explanted devices must be immediately put into neutral buffered 10% formalin for tissue fixation and returned to the sponsor OstomyCure for evaluation.

6.17. Withdrawals or Discontinuation

6.17.1. Lost to Follow-Up Subject

A subject will be considered “lost to follow-up” and terminated from the study when all of the following criteria have been met.

- Failure to complete 3 consecutive visits without due cause (after 30 days)
- Documentation of 3 unsuccessful attempts, one of which must be in written communication, by the Investigator or his/her designee to contact the subject or next of kin
- A communication from the Investigator to Sponsor reporting subject as lost to follow up
- Subjects lost to follow up will still require management of their stoma and they will be in contact with their standard stoma team for the continuing management of their stoma.

6.17.2. Withdrawal

Subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up. The reason for withdrawal will be recorded (if given) in all cases of withdrawal. The investigator may discontinue a subject from participation in the study if the investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. No new data will be collected after withdrawal from the study. Data that have already been collected on withdrawn subjects will be retained and used for analysis, unless disallowed by national or local regulations.

6.17.3. Unplanned pregnancy

In the event that any subject becomes pregnant during the study, the pregnant subject will be withdrawn from the study. The optimal way to handle the implant will be reviewed on a case by case basis involving the investigator, obstetrician and the subject. No new data will be collected after withdrawal from the study. Data that have already been collected on

withdrawn subjects will be retained and used for analysis, unless disallowed by national or local regulations.

6.17.4. Study Completion

All subjects will be evaluated at discharge from hospital, 4 weeks, 8, 16, 24, 36 and 52 weeks post implantation procedure. A subject's participation in the study will be considered complete after the 52-week visit.

7. RISK-BENEFIT ANALYSIS

7.1. Risks Assessment and Risk Mitigation

7.1.1. Risks Associated with ileostomy

Creation of a stoma is a well-established surgical technique and should only be carried out by a surgeon experienced in this procedure. The risks are well known and are reported in the published literature. They can be discussed according to time to onset. As a consequence of the complications listed below, the patient may require medical or surgical intervention, including re-operation.

Complications with onset within 30 days following ileotomsy

- High output leading to dehydration/electrolyte abnormalities
- Ischemia/necrosis of the stoma
- Edema and venous congestion of stoma
- Retraction of stoma
- Technical complications
- Risk of recurrence in patients with Crohn's disease

Complications with onset after 30 days following ileotomsy

- Peristomal skin complications
- Retraction of stoma
- Parastomal Hernia
- Mucocutaneous separation
- Peristomal pyoderma gangrenosum
- Stenosis
- Intestinal obstruction
- Technical complications
- Peristomal suppuration and fistula formation – Crohn´s disease is associated with a higher risk.
- Recurrence of disease activity in patients with Crohn's disease

7.1.2. Risks Associated with the procedure of Implantation of the TIES® Port

Potential risks associated with implantation of the TIES® Port are described here, note that some of these complications are known complications of ileostomy. As a result of the complications listed below, the patient may require medical or surgical intervention, including re-operation and/or removal or replacement of the TIES® Port.

- Redness at the operation site
- Pain

- Allergic reaction (including to medications, anaesthesia or device materials)
- Infection
- Device misplacement or displacement
- Enterocutaneous fistula
- Perforation of the intestine during insertion of ileum through implant
- Contamination of implant with intestinal content during surgery
- Narrow passage caused by irritated or swollen intestine
- Occlusion, sub-occlusion and constipation
- Parastomal/incisional hernias

7.1.3. Possible Risks Related to the TIES® Port, including Functional Risks

7.1.3.1 ***Titanium as a biocompatible material***

The titanium used to manufacture the implant is a medically approved material that has been used in surgery for more than 30 years. Titanium is recognized to be non-allergenic. Various tests in line with regulatory standards have been performed during the development to ensure bio-compatibility of the TIES® Port with human tissue.

7.1.3.2 ***Potential risks post-surgery***

It is important to maintain the TIES® Port in place during the healing period to facilitate tissue ingrowth into the implant in the abdominal wall and avoid applying any stress to the TIES® Port. Possible risks that may arise include:

- Insufficient ingrowth of soft tissue into the TIES® Port to ensure a leak-free system
- Leakage of intestinal liquid between the device and the skin due to:
  - Ileum retraction
  - Too early use of the TIES®Lid
  - Trauma
  - Other factors
  - External violence - skin or body injuries caused by the protruding part of the implant getting caught or by violent accidents

7.1.3.3 ***Actions required if ingrowth is insufficient***

Should the system show incomplete ingrowth inside or outside or being harmed in a way or other over time, it should be “put to rest”. The usage of the TIES® Lid should be stopped for a few weeks to give the biological system time to adjust to the situation and come to a new balance; the ingrowth of the skin and the intestinal serosa and mucosa tends to adjust by itself.

7.1.4. Possible Risks Associated with the Post-Operative Care of the TIES® Port

All post-operative stoma care procedures are standard procedures and are not expected to add any additional risk. There are no additional risk-baring procedures planned in the study (e.g. CT-Scan, X-rays).

Warnings and Precautions are included in the Surgical Procedure Manual and in the User Care Manual (see Appendix).

7.1.5. Possible Risks and Side Effects Associated with Medication

The patients may continue to take their usual medication as required. There is no additional medication required for the TIES® Port implantation procedure, other than that usually used to perform a common end ileostomy.

There is no known incompatibility between the TIES® System and any medication.

7.1.6. Risks Mitigations

Risk mitigation in this study will be accomplished through the following actions:

- Clear definition of inclusion/exclusion criteria to ensure only appropriate subjects are enrolled, in line with contraindications listed in the Surgical Procedures Manual
- Ensuring that treatment and follow-up of the subject is consistent with current medical practices
- Selection of investigators who are experienced and skilled in performing ileostomy procedures
- Completion of training of site personnel by the Sponsor
- Performing all procedures in accordance with the Surgical Procedure Manual and User Care Manual
- Device training to the patient, per the User Care Manual
- Advise the patient on good care of the stoma and regular review by Stoma/ Research nurse
- Advise the patient on specific dietary measures to avoid excessive output
- Use of only soft catheter and soluble gel for intestinal emptying (flushing), to avoid occlusion, sub-occlusion and constipation
- Continuous safety review processes

7.1.7. Residual risks

There are known long-term risks associated with ileostomy. These include peristomal skin complications, retraction of stoma, incisional or parastomal hernia, mucocutaneous separation, intestinal obstruction, infection, fistula formation, or recurrence of the background disease. The presence of the implant is unlikely to alter the occurrence of these conditions and they can be treated using standard medical practice. It is expected that the study subjects will be followed up life-long in clinics specialised in care of stoma patients.

7.2. Benefit Assessment

7.2.1. Potential Benefits of the TIES® System

- Patient controlled continent ileostomy
- Fewer or no stoma bags needed
- Better quality of life (ability to travel, better social integration)
- Facilitated manipulation (clean and comfortable evacuation)
- Facilitated body hygiene
- No skin irritation resulting from stoma fixation device
- A leak-free system – “accidents” becoming a non-issue

7.2.1. Risks to Benefit Rationale

The product development and risk management activities for the TIES® System were performed while considering the essential requirements of the European Medical Device Directive (MDD) 93/42/EEC. Pre-clinical testing was performed using animal models and *in vitro* testing, before conducting clinical investigations in human subjects. Ostomycure AS has established manufacturing controls following the requirements of ISO 13485.

The potential risks outlined above will be mitigated by proper patient selection, the attention given to the choice of investigational sites, the expertise of the investigators and surgeons, regular review by stoma/research nurse, and the training that will be provided to all involved study personnel, and to the patients.

It is noted that following any explantation/removal of the device, the patient can revert to use of ileostomy bags without any added risks.

The potential benefits of the system outweigh the potential risks, supporting use of the TIES® System in this study.

8. ADVERSE EVENT MANAGEMENT

Subjects will be carefully monitored during the study for possible adverse events (AEs) from the time the subject signs the Patient Informed Consent form to the completion of their participation in the study. Any AE observed will be fully investigated by the Investigator and classified in line with the definitions of the ISO14155:2011 as described below.

8.1. Definitions

Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

NOTE 1 This definition includes events related to the investigational medical device or the comparator.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

Treatment emergent adverse events are adverse events with onset at or following the implantation procedure for the purpose of this study.

Serious Adverse Event (SAE):

Adverse event that:

a) led to death,

b) led to a serious deterioration in the health of the subject, that either resulted in

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) hospitalization or prolongation of existing hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to foetal distress, foetal death or a congenital abnormality or birth defect

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.

Device Deficiency:

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Adverse Device Effect (ADE):

Adverse event related to the use of an investigational medical device

NOTE 1 This definition includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, implantation, installation, operation, or any malfunction of the investigational medical device.

NOTE 2 This definition includes any event resulting from a use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE):

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

Unanticipated Serious Adverse Device Effect (USADE):

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Use error:

Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

NOTE 1 Use error includes slips, lapses, and mistakes.

NOTE 2 An unexpected physiological response of the subject does not in itself constitute a use error.

Malfunction:

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

8.2. Event severity

Event severity is classified as follows:

Mild: awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae

Moderate: interferes with the patient's usual activity and/or requires symptomatic treatment

Severe: symptom(s) causing severe discomfort and significant impact on the patient's usual activity and requires treatment

8.3. Causality relationship

The investigator will assess the causality of all adverse events in relation to the research, i.e., the relationship between the AE / SAE and the investigational treatment or any other study-related procedures.

Each SAE will be classified according to five different levels of causality:

1) Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has no temporal relationship with the use of the investigational device or the procedures;

- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;

- the event involves a body-site or an organ not expected to be affected by the device or procedure;

- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

- harms to the subject are not clearly due to use error;

- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has a temporal relationship with investigational device use/application or procedures;

- the event involves a body-site or organ that

- the investigational device or procedures are applied to;

- the investigational device or procedures have an effect on;

- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);

- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;

- harm to the subject is due to error in use;

- the event depends on a false result given by the investigational device used for diagnosis, when applicable

- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

8.4. Investigator Reporting Responsibilities

The investigator should report to the sponsor the following events, whether expected or not, in the corresponding CRF form, with the exception of AEs / SAEs detected before the patients has signed the patient consent form.

- AE
- SAE
- Device Deficiencies that did not but might have led to a SAE if:
    - Suitable action has not been taken or
    - Intervention had not been made or
    - If circumstances had been less fortunate
- New findings/updated in relation to already reported events

If an AE / SAE is present at the beginning of study prior to the subject providing signed consent to participate in the study, only its worsening should be reported.

The investigator will document all AEs on the Adverse Event Form, including (at a minimum) a description of the event, date of onset, severity, relationship to the investigational device and/or procedure, required interventions, duration, and outcome. The investigator will monitor all AEs until they are resolved, determined to be a chronic condition or the subject is lost to follow-up. The investigator will report all AEs regardless of whether it is anticipated or unanticipated and regardless of classification, seriousness, intensity, outcome or causality.

All Serious Adverse Events including all device deficiencies that could have led to a SAE should be reported to the Sponsor within 24 hours of awareness of an event via the Adverse Event electronic Case Report Form in the study's electronic database, as that will trigger an immediate e-notification to the Sponsor and Devicia. All device deficiencies should also be reported without unjustified delay.

If the e-CRF is unavailable, notification to the sponsor can be made by email and the email address is TIESstudy@ostomycure.com

The investigator must ensure that all additional relevant information (i.e., radiology reports, hospitalization reports indicating the SAE) that becomes available is also forwarded to the sponsor immediately after the initial notification and the information should be de-identified.

8.5. Reporting to Ethic Committee / Competent Authority

Depending on the local requirements or following agreement between both parties, the sponsor or the principal investigator will be responsible for performing safety reporting to the Ethics Committee according to the relevant local regulatory requirements.

Devicia will be responsible for reporting to the National Competent Authority according to national requirements and in line with MEDDEV 2.7/3.

The sponsor must report to the national Competent Authorities where the clinical investigation has commenced:

- a SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons11 or a new finding to it: immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
- any other reportable events as described in section 8.1 or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

9. DATA SAFETY MONITORING BOARD

An independent committee comprised of experts in the field of gastroenterology or colorectal surgery will review all the safety and performance data on at least 2 occasions during the study:

(1) The first review will take place after the first 5 subjects have been implanted and the fifth subject has been followed to 8 weeks. The purpose of the review of data to 8 weeks is to make recommendations if changes to the study design would be required. This meeting should be held about 4 weeks after the data becomes available.

(2) The second review is planned after collection of 24-week results from the first 20 subjects to review if further modification to the collection of outcome measurements for performance assessment would be required.

In the event of reports of unexpected adverse events, an independent expert will review these unexpected adverse events and making assessment in regards of the seriousness and relationship to the device.

10. STATISTICAL CONSIDERATIONS

10.1. Objective of the study

This is a single-arm prospective multi-center clinical study to evaluate the safety, performance, durability of TIES® Port in patients who require permanent ileostomy as its

primary objective, and assessment of impact on quality of life in the implanted patients as its secondary objective. Acceptability of the TIES® solution for patients will is part of assessment of performance.

For patients who require a permanent ileostomy, the current available alternatives for emptying of ileal contents are (1) attaching a stoma bag to the end-ileostomy; (2) surgery to create a pelvic pouch through an ileo-anal anastomosis; and (3) surgery to create a continent ileostomy. All of these procedures are associated with complications and failure rates.

The TIES® solution is intended as an alternative to stoma bags in patients requiring end-ileostomy so that the patient has control over emptying of intestinal wastes and to minimise the need to wear stoma bags for collection and emptying of intestinal wastes. This is achieved by putting a TIES® Lid on the TIES® Port to control emptying of intestinal waste through the Port, instead of letting the waste emptiy continuously into a stoma bag. In addition, the TIES® solution can also be an option for patients who cannot tolerate use of stoma bags due to complications, failed continent ileostomy or failed pelvic pouch.

10.2. Study design

This protocol plans for five interim data analyses during the course of this open study. The first two interim analyses are planned after collection of 8-week results from the first 5 and of 24-week results of the first 20 subjects, respectively, to review all available study data and to assess if there is a need to modify the study protocol including adjusting the collection of outcome measurements for performance assessment. The third, fourth and fifth interim analyses will be conducted when 50, 100 and 150 subjects, respectively, have completed 24 weeks follow-up in order to assess the primary and secondary 24-week safety and performance endpoints, make a preliminary assessment of the types of patient with high device acceptability, and consider whether some of the secondary study instruments (e.g. Quality of Life Questionnaires) can be dropped on the remaining patients to simplify follow-up and reduce burden on patients and clinical teams.

10.3. Study Population Definition

The study population is defined according to the Intent-to-Treat principle. All enrolled subjects will be taken into consideration in the reported results, without any planned exclusion.

10.4. Performance Evaluation

The subject is assumed to empty the “bowels” about 6 times per day. 6-months is chosen as the time point for primary endpoint assessment because the subject is expected to be familiar with the use of the TIES® Lid as well as study procedures at that time.

- By analysing the frequency of use of the TIES® Lid versus the use of stoma bags in individual subjects, this gives an assessment of the usefulness and acceptability of the TIES® solution.
- Leakage around the stoma between emptying is to be assessed. For a conventional end-ileostomy, the peristomal skin is often in contact with the intestinal contents and at least 30% of the patients reported skin problems based on the literature. For patients with pelvic pouch, perfect continence is achieved in less than 80% of patients.

Performance evaluation is based on subject´s assessment of performance as recorded on the 3-day diary preceding each scheduled follow-up at 16, 24, 36 and 52 weeks after

operation. Performance evaluation applies only among subjects with the TIES® Port *in situ.*

Among subjects with the TIES® Port *in situ,* performance will be assessed according to (a) the proportion of subjects who use the TIES® Lid for continence control; (b) the proportion of subjects experiencing visible leakages around the implant; and (c) subject´s assessment on the ease of use of the TIES® Solution.

Primary endpoint is absence of visible leakage or fecal staining of clothing at 24 weeks after implantation of the TIES® Port.

The success criterion at 24 weeks requires at least 70% of subjects with the TIES® Port *in situ* having no visible leakage or staining of clothing adjacent to the implant between consecutive episodes of using the lid for continence control. Spillage that might occur at opening of the lid is not regarded as leakage.

Secondary endpoints are

- Absence of visible leakage or fecal staining of clothing at 16, 36 and 52 weeks.
- Proportion of implanted subjects using the TIES® Lid for continence control at 16, 24, 36 and 52 weeks.
- Subject´s assessment on the ease of use of the TIES® Lid using a visual analog scale 16, 24, 36 and 52 weeks after implantation.
- Subject´s preference for the TIES® solution assessed at 52 weeks.

The subject´s assessment on the ease of use of the TIES® Lid will provide feedback to the manufacturer regarding future refinements of the TIES® solution. Information will be collected in the diary to understand patient´s needs and the number of stoma bags used as described in section 10.

10.5. Sample size

The purpose of the study is to assess the durability and performance of the TIES® Port over one year. The table below shows the power to demonstrate non-inferiority to within 10% of the target 24-week performance criterion of 70% of subjects with the device *in situ* experiencing no leakage (i.e. lower two-sided 95% confidence limit no less than 60%) according to the true proportion and number of assessable subjects.

True proportion experiencing no leakage at 24 weeks	200 subjects	180 subjects	160 subjects	140 subjects	120 subjects
70%	87%	83%	79%	73%	67%
71%	93%	90%	87%	82%	76%
72%	97%	95%	92%	89%	83%
73%	99%	98%	96%	93%	89%
74%	99%	99%	98%	97%	94%
75%	100%	100%	99%	98%	97%

There will be sufficient power with the planned 200 subjects to demonstrate non-inferiority of the TIES® Port with respect to the primary performance criterion (efficacy when device used as intended), if at least 80% of subjects are evaluable at 24 weeks (i.e. with at least 160 subjects). If the true proportion of patients experiencing no leakage is higher than the expected minimum of 70% there will be sufficient power to demonstrate non-inferiority even with fewer than the expected proportion of evaluable subjects at 24 weeks.

10.6. Durability Evaluation

Durability of use is evaluated by the cumulative proportion of subjects with the TIES® Port *in situ* at each of the following timepoints of 8,16, 24, 36 and 52 weeks. These are secondary endpoints.

Durability will be computed by lifetable methods as the complement of the cumulative proportion of subjects in whom the TIES® Port has been removed or has spontaneously explanted, with subjects censored if they withdraw from the study with the device *in situ*, have insufficient follow-up time, or the device is removed for reasons unrelated to device performance.

10.7. Safety Evaluation

Safety outcome measures are secondary endpoints and will be analysed as proportion of all implanted subjects using descriptive statistics. Safety information will be collected during the following intervals: during hospitalisation, interval from discharge to 4-weeks visit, interval after the 4-weeks visit including 8-weeks visit, interval after the 8-weeks visit including 16-weeks visit, interval after the 16-weeks visit including 24-weeks visit, interval after the 24-weeks visit including 36-weeks visit, and interval after the 36-weeks visit including 52-weeks visit.

Secondary endpoints are:

- Proportion of implanted subjects with treatment emergent adverse events. Treatment emergent adverse events are defined as events with onset during or after the implantation procedure.
- Proportion of implanted subjects with peristomal skin lesions will be evaluated using a validated 5-point scale by assessing signs of erythema, erosion, or papular lesions.
- Proportion of implanted subjects with device-related adverse event.
- Proportion of implanted subjects with device displacement, device revision or device replacement.

Photographs of the stoma are to be taken to document the ingrowth into the TIES® Port, surrounding peristomal skin and position of the implant at 4, 8, 16, 24, 36 and 52 weeks after implantation. At least 4 views are to be taken: horizontal, vertical frontal, vertical right and vertical left. Additional views may be required if skin lesions or device displacement develop.

The adverse events complicating end-ileostomy, continent ileostomy and pelvic pouch are well described in the literature. Adverse events known to complicate end-ileostomy include peristomal skin problems, infection, abscess, entero-cutaneous fistula, necrosis, stenosis, prolapse, retraction, parastomal hernia, incisional hernia, obstruction to emptying of intestinal contents. That said, the exact incidences are unknown because many reports are retrospective and the experience of the site may influence the outcomes.

All adverse events, device-related complications and device deficiencies or malfunctions described in section 4 will be fully summarized. Adverse events are to be assessed for seriousness and causality.

For all definitions indicated in section 10.1, the total number of adverse events, percentage of subjects with at least one given adverse event (AE, ADE, SAE, SADE, USADE) will be reported in summary tables. Moreover, description of events will be presented in listings. Severity and relationship will be documented for all defined adverse events (AE, ADE, SAE, SADE, USADE).

10.7.1. Peristomal skin lesions

Peristomal skin lesions are common and the incidences range from 20% to 50%. Dermatoses included irritant reactions, particularly from leakage of urine or feces and pre-existing skin diseases, infections, allergic contact dermatitis, and pyoderma gangrenosum are less common. The classification of Borglund will be used to assess severity of the skin lesions the site. Photographs of the stoma and skin lesions will be taken as part of study documentation and for review by an independent panel if required.

Classification of peristomal skin complications (Borglund et al)

Category	Criterion	Additional explanation
E0/P0	No signs of irritative skin lesions; no obvious signs of erythema, erosion, or papular lesions	
E+/P0	Mild erythematous-erosive skin lesions E+/P0	This subgroup (E+) includes patients with dispersed papules lesions, and/or tiny, erythematous, macular lesions, vesicles, or tiny erosion.
E++/P0	Severe erythematous-erosive skin lesions.	The E++ subgroup includes patients with numerous papules and/or tiny macules, confluent erythematous macules, widely spread erosions, excoriations, and ulcerations.
E0/P+	Mild pseudoverrucous skin lesions	The mild (P+) pseudoverrucous skin lesion is characterized by dispersed, single, eruptive, or partly confluent, wart-like papules, or nodules located on the peristomal skin close to the mucocutaneous lining.
E0/P++	Severe pseudoverrucous skin lesions	The P++ reflects severe pseudoverrucous skin lesions and is a confluent, elevated ostomy circumference close to the ostomy mucosa.

10.8. Quality of Life Evaluation

Impact on quality of life will be evaluated by using two validated instruments EQ-5D-5L Quality of Life (QoL) questionnaire and Montreux Quality of Life questionnaire.

Secondary endpoints are:

Change in quality of life from baseline at 8, 16, 24, 36 and 52 weeks post implantation will be assessed among subjects with the device *in situ*.

10.9. Statistical analysis

Statistical analyses will be done using SAS System®, Version 9.2 or further and a complete statistical analysis plan will be written before the conduct of analysis. All statistical analyses will be made on locked databases following data clarifications resolved due to Data Management process.

No replacement of missing data is planned in the statistical analysis.

No statistical testing will be conducted for any other parameters in the study and only descriptive analysis will be provided to fully describe the parameters recorded.

Continuous variables will be summarized using standard quantitative statistics: number of non-missing observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations will also be specified.

Categorical variables will be summarized using classical frequency statistics: number of non-missing observations and percentages by categories. Percentages will be calculated on the number of non-missing observations. The number of missing observations will also be specified.

Durability of use will be analysed using lifetable methods to allow for censoring due to subject withdrawal and device removals for reasons unrelated to device performance.

Two-sided 95% confidence intervals will be computed for all primary and secondary endpoints.

A statistical analysis plan will be written to describe all derived variables used in the reporting (especially for all parameters to be compared in time: EQ-5d and Montreux QoL questionnaire) and the statistical tables and listings to be generated.

10.10. Additional analyses

10.10.1. Photographs of the stoma and adjacent skin

Photographs of the stoma are to be taken to show the ingrowth into the implant and the peristomal skin at discharge, 4, 8, 16, 24, 36 and 52 weeks as described in section 6.
The extent of ingrowth will be estimated using the following scale at skin/device junction and ileum device junction:

1. Complete
2. Partial
3. None

An independent review of skin lesions will be performed by a dermatologist if required.

10.10.2. Use of stoma bags

It should be noted that subjects will need to use stoma bags for at least the first 12 weeks until the TIES® Lid can be used regularly, and probably also during sleep after that period. Information on the continuous use of stoma bags during sleep based on recall will be recorded in subject´s diaries at 16, 24, 36 and 52 weeks and will be presented using summary statistics.

10.10.3. Subject´s preference

Because the subjects will need to use stoma bags continuously for at least the first 8 weeks and then intermittently until the TIES® Lid can be used regularly, it is of interest to obtain their assessment on how the two alternatives may influence their wellbeing. Four topics from the 2 quality of life questionnaires have been selected for comparisons. This assessment will be performed at the last study visit at 52 weeks. The subjects will be asked the following questions about their experience with the use of the TIES® Solution compared to the continuous use of stoma bags.

1. Regarding maintaining body hygiene
a) No difference with using either stoma bags that collected waste continuously or TIES® Lid for periodic emptying of waste
b) Easier with stoma bags that collected waste continuously
c) Easier with TIES® Lid for periodic emptying of waste

2. Regarding daily activities (e.g. work, study, housework, family or leisure activities)
a) No difference with using either stoma bags that collected waste continuously or TIES® Lid for periodic emptying of waste
b) Easier with stoma bags that collected waste continuously
c) Easier with TIES® Lid for periodic emptying of waste

3. How worried were you about odor from your stoma?
a) No difference with either stoma bags that collected waste continuously or TIES® Lid
b) Less worry with stoma bags that collected waste continuously
c) Less worry with TIES® Lid for periodic emptying of waste

4. How worried were you about leakage from your stoma?
a) No difference with either stoma bags that collected waste continuously or TIES® Lid for periodic emptying of waste
b) Less worry with stoma bags that collected waste continuously
c) Less worry with TIES® Lid for periodic emptying of waste

5. Would you recommend the TIES® solution to friends or family members who need to undergo ileostomy?
a) No
b) Undecided
c) Yes

11. GENERAL STUDY CONSIDERATIONS

11.1. Ethical and Regulatory Considerations

The study will be performed in accordance with the standard EN ISO 14155 on clinical investigations with medical devices and Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki) adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

The clinical investigational plan, informed consent, any other specific study documents and all amendments to these study documents will be reviewed and approved by the Ethics Committees (ECs) and Competent Authority/ies (CAs) if appropriate before enrolment of any patient.

Any additional requirements by the EC or CA will be followed.

11.2. Amendments

The IB, CIP, CRFs, informed consent form and other subject information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the CIP shall be agreed upon between the sponsor and principal investigator, or the coordinating investigator. The amendments to the study documents shall be notified to, or approved by, the EC and regulatory authorities, if required. The version number and date of amendments shall be documented.

11.3. Protocol Deviations

The Principal Investigator is required to conduct the study in accordance with the signed clinical trial agreement/investigator agreement and the clinical protocol. However in some situations protocol deviations will occur.

Protocol deviations are defined as instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. Unders emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

The Principal Investigator shall promptly report any deviations from the CIP that affects the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances. The Principal Investigator shall notify the Sponsor in writing, no later than 24 hours after significant deviation from the study plan, to protect the life or physical wellbeing of a subject in an emergency.

When specific tasks are delegated by the Principal Investigator, included but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory deviations resulting from failure to adequately supervise the conduct of the clinical study.

Protocol deviations also include, but are not limited to:

- Examinations/test/assessment not performed within the allowed follow-up window
- Required data not obtained

The study site should report the protocol deviation on the applicable CRF page.

Protocol deviations will be reported in progress reports to CA and EC where applicable and within other required timelines.

Investigators that show continued, serious failings in adherence to the CIP, inspite of apropriate corrective and preventive actions will be disqualified from the study.

11.4. Data handling and Record Keeping

11.4.1. Data Collection, Processing and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by CRFWEB eCRF provider Clindox. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the Sponsor or its representative. The software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate eCRFs in compliance with local regulations.

Manual and/or automatic queries will be created in the EDC system and will be issued to the center for appropriate response. Site staff will be responsible for resolving all queries in the database.

11.4.2. Data Retention

The Investigator will maintain at the investigative centre in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 10 years have elapsed since the formal discontinuation of this study. These documents will be retained for a longer period by agreement with the Sponsor or in compliance with other local regulations. It is the Sponsor's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and the Sponsor must receive written notification of this custodial change.

11.5. Monitoring

Monitoring will be performed during the study according to the monitoring plan to assess continued compliance with the protocol and applicable regulations. In addition, the monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original source documents by the Sponsor, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by the Sponsor or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

11.6. Insurance

Subjects who participate in this study will be insured against study related injury according to local regulations requirements.

The Sponsor has issued clinical trial insurance with appropriate coverage for the continuation of the entire study.

11.6.1. Suspension or premature Termination

The Sponsor reserves the right to suspend or terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated ECs, and regulatory authorities will be notified in writing in the event of study suspension or premature termination along with reasons for the actions taken/decisions made.

Possible reasons for study suspension or premature study termination include, but are not limited to, the following:

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrolment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of the Sponsor to suspend or discontinue development of the device.

11.6.2. Criteria for Suspending/Terminating a Study Site

The Sponsor reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study devices and testing equipment, as applicable, will be returned to the Sponsor unless this action would jeopardize the rights, safety or wellbeing of the subjects. The EC and regulatory authorities, as applicable, should be notified. All subjects enrolled in the study at the site will continue to be followed per this protocol. The Principal Investigator at the site must make provision for these follow-up visits unless the Sponsor notifies the investigational centre otherwise.

11.6.3. Procedure for resuming the clinical investigation after temporary suspension

When the sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor shall inform the principal investigators, the ECs, and, where appropriate, the regulatory authority of the rationale and provide them with the relevant data supporting this decision.

Concurrence shall be obtained from the ECs and regulatory authorities before the clinical investigation resumes.

If subjects have been informed of the suspension, the principal investigator or authorized designee shall inform them of the reasons for resumption.

11.7. Publication Policy

At the end of the trial, a Clinica Investigation Report will be compiled. At the conclusion of the trial, a multi-centre manuscript will be prepared for submission to a peer reviewed scientific journal, within 6 months after database lock. The publication of the principal results from any single centre experience within the trial can be initiated only after the publication of the multi-centre results, unless a decision is made not to pursue a multicentre manuscript. Any exceptions to this would require the prior written approval of the Sponsor.

Investigators may publish study results, provided Sponsor receives a copy of any proposed oral presentation or written publication at least 10 working days in advance of submission for presentation or publication for review. Sponsor has the right to comment on the appropriateness of the data analysis and presentation. Investigator will meet with Sponsor prior to submission for publication for the purpose of making good faith efforts to discuss and resolve any issues or disagreement. Upon Sponsor's request, Investigator shall remove from any such oral presentation or written publication any commercial-in confidence information.

11.8. Funding and agreements

This investigation is funded by OstomyCure AS. A clinical investigation agreement is set between the sponsor and each invetigatioal site, detailing roles and responsibilities.

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13. APPENDICES

Appendix A: Surgical Procedure Manual
Appendix B: User Care Manual
Appendix C: Patient´s guide for the first 16 weeks after implantation
Appendix D: Montreux Quality of Life Questionnaire
Appendix E: EQ-5D-5L Quality of Life Questionnaire
Appendix F: Subject´s Diary on Use of the Implant
Appendix G: Subject´s Preference Questionnaire
Appendix H: Study sites list

Appendix	Document name	Sponsor Document number for English version
Appendix A	Surgical Procedure Manual	31-5TF12033-17
Appendix B	User Care Manual	31-5TF17062-05
Appendix C	TIES® C03 Patient´s guide for the first 16 weeks after implantation	73-2CL17003-03
Appendix D	TIES® C03 Subject´s Diary on Use of the Implant	73-2CL17004-03
Appendix E	TIES® C03 Subject´s Preference Questionnaire	73-2CL17005-01
Appendix F	TIES® C03 Montreux Quality of Life Questionnaire	73-2CL17006-01
Appendix G	TIES® C03 EQ-5D-5L Quality of Life Questionnaire	73-2CL17007-01