TRX Orthopaedics
Limited

OrthoPure® XT Ligament Reconstruction Implant

Summary of Safety & Clinical Performance

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions for Use (IFU) as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

1. Device identification and general information

1.1. Device trade name(s)

OrthoPure® XT

1.2. Manufacturer; name and address

TRx Orthopaedics Limited

Unit 3 Phoenix Court

Lotherton Way

Garforth

Leeds

LS25 2GY

UK

1.3. Manufacturer single registration number (SRN)

GB-MF-000018091

1.4. Basic UDI-DI

506026002XT001WA

1.5. Medical device nomenclature description / text

P0910: Implantable prosthetic and osteosynthesis devices – Ligament prostheses

1.6. Class of device

Class III

1.7. Year when the first certificate (CE) was issued covering the device

2020

1.8. Authorised representative name and the SRN

Advena Limited

Tower Business Centre

2nd Floor

Tower Street

Swatar

BKR 4013

Malta

SRN: MT-AR-000000234

1.9. NB's name (the NB that will validate the SSCP) and the NB's single identification number

BSI Group The Netherlands B.V.

Say Building,

John M. Keynesplein 9,

1066 EP Amsterdam,

The Netherlands

NB #2797

2. Intended use of the device

2.1. Intended purpose

The intended use of OrthoPure® XT is for reconstruction of knee ligaments to restore knee function and stability.

2.2. Indication(s) and target population(s)

Indication	**Patient Population**
Primary anterior cruciate ligament (ACL) reconstruction where autograft is not suitable	Patients suffering a tear/rupture of the ACL
Revision ACL reconstruction	Patients suffering a tear/rupture of the ACL who have already undergone ACL reconstruction in the affected knee
Multi-ligament reconstruction	Patients suffering a tear/rupture of at least two of the four major knee ligament structures

2.3. Contraindications [or restrictions for use] and/or limitations

OrthoPure® XT has the following contraindications:

- Not to be used for primary ACL reconstruction in high demand patients or those under 35 years of age.
- Not to be used if severe pain, swelling or redness at the surgery site is observed within 24 hours prior to surgery.
- Not to be used if active systemic infection, or local infection at the surgery site. This includes all cases of septic arthritis, and where there is a risk of secondary infection such as an open wound of the joint.
- Patients with known allergy, hypersensitivity or religious objection to the use of implanted porcine material.
- Patient who is unable or unwilling to follow post-operative care and rehabilitation programme.

3. Device description

3.1. Description of the device

The OrthoPure® XT device is an acellular, sterile, single use porcine tissue scaffold that is manufactured using a proprietary decellularisation process that renders the tissue free from cells, leaving the porcine tissue biocompatible, and safe for implantation into the knee.

The device is provided sterile, being sterilised by gamma irradiation, and presented in double blister packs containing the graft(s) in 0.9 % physiological saline. Each device is packed in a tertiary box alongside an IFU, six patient record labels, an implant card and instruction leaflet pertaining to the implant card.

An illustration of OrthoPure® XT is provided in Figure 1.

Figure 1: OrthoPure® XT device in packaging

OrthoPure® XT is integrated by the body following implantation. The decellularised tissue material provides an 'extracellular collagen matrix' (ECM), which facilitates a remodelling process, whereby the host cells infiltrate the scaffold post implantation. The remodelling process occurs during rehabilitation.

The OrthoPure® XT device does not contain a medicinal product, human blood products, or materials of human origin.

OrthoPure® XT is available in four sizes. Details of the configurations are presented in Table 1.

Table 1: OrthoPure XT product sizes and configurations

Size	Configuration	Minimum product length when doubled over	Graft diameter when doubled over
5	A single tendon in a blister pack	120 mm	5-6 mm
6	A single tendon in a blister pack	120 mm	6-7 mm
8	Two single tendons in one blister pack	120 mm	8-9 mm (when two tendons are sized together (4 strands))
10	Three blister packs provided (a single tendon in each blister pack)	120 mm	9.5-11 mm (when three tendons are sized together (6 strands))

Note: The device can be trimmed to length in the surgical environment as required.

Device Materials

OrthoPure® XT does not contain materials of concern (MOC) greater than 0.1% (w/w), carcinogenic, mutagenic or toxic to reproduction (CMR), or endocrine-disrupting substances.

OrthoPure® XT does not contain substances or combinations of substances that are absorbed by or locally dispersed in the human body.

OrthoPure® XT device materials and type of patient contact are summarized in Table 2.

Table 2: Materials of Construction

Component	Materials	Type of contact with body
~32%	Porcine derived collagen	Direct via implantation
~68%	Moisture	Direct via implantation

3.2. A reference to previous generation(s) or variants if such exist, and a description of the differences

There are no previous generations of OrthoPure® XT.

3.3. Description of any accessories which are intended to be used in combination with the device

There are no accessories provided with the device.

3.4. Description of any other devices and products which are intended to be used in combination with the device

The devices which OrthoPure® XT may be used in conjunction with are analogous to those which would be used in conjunction with soft tissue grafts for the same indications.

No instructions/recommendations to use OrthoPure® XT with other specific devices are given.

4. Risks and warnings

4.1. Residual risks and undesirable effects

The identified residual risks associated with OrthoPure® XT are as follows:

- Device biocompatibility;
- Use of animal derived material:
- Packaging system;
- Terminal sterilisation process;
- Device performance;
- Device stability;
- Labelling, warnings, and contraindications;
- Surgical technique and post-operative care.

These residual risks are disclosed in the OrthoPure® XT IFU via the warnings & precautions, contraindications, undesirable side-effects and potential adverse events.

Identified undesirable effects, potential risks & adverse events associated with OrthoPure® XT as documented in the current IFU are detailed in Table 3.

Table 3: OrthoPure XT undesirable effects

Undesirable side effects, potential risks & adverse events as disclosed in the IFU	**Reported in State-of-the-art Literature**	**Reported for OrthoPure XT** *[pre-market clinical data and PMCF activities for isolated primary ACL reconstruction indication]*		**Reported in OrthoPure XT PMS (Complaints) data**
		2 years *[% of cohort affected (n), no. of events]*	**5 years** *[% of cohort affected (n), no. of events]*	
Graft rupture/failure	Primary ACL reconstruction Revision/rupture at any post-operative time-point: 8.8 %[1] Revision rate as defined by registry data: Up to 14 %[2] Revision ACL reconstruction Revision/rupture rate: 14.8%[1] Multi-ligament reconstruction Revision/rupture rate: 3.37%[1]	10% (4/40), 4	17.5% (7/40), 7	None reported
Residual laxity and symptoms of joint instability	As assessed by the following performance objectives of measurement: • KOOS[3] [pain, symptoms, function in daily living, function in sports and knee related quality of life subsets] • IKDC[4]			None reported
KOOS - Pain	91.06	97.5	97	
KOOS - Symptoms	83.52	96.5	93	
KOOS - Function in daily living	96.76	99.2	98	
KOOS - Function in sports	82.52	92.7	89	

[1] Weighted average determined from state-of-the-art literature
[2] As not all failures are revised, the revision rate may be lower than the failure rate.
[3] Knee Injury and Osteoarthritis Outcome Score
[4] International Knee Documentation Committee

Undesirable side effects, potential risks & adverse events as disclosed in the IFU	**Reported in State-of-the-art Literature**	**Reported for OrthoPure XT** *[pre-market clinical data and PMCF activities for isolated primary ACL reconstruction indication]*		**Reported in OrthoPure XT PMS (Complaints) data**
		2 years *[% of cohort affected (n), no. of events]*		**5 years** *[% of cohort affected (n), no. of events]*	
Residual laxity and symptoms of joint instability *(continued)*	*Per previous page*				*Per previous page*
KOOS - Knee related quality of life	71.12	80.9		84	
IKDC	85.01	91.1		93	
Intraoperative complications	No specific rates reported in clinical literature for intraoperative complications during knee ligament reconstruction surgery.	**0% (N=0/40), 0**		**0% (N=0/40), 0**	None reported
Surgery-related complications e.g. – Pain and/or numbness – Knee laxity – Limited knee range of motion – Crepitus – Kneeling discomfort – Osteoarthritis/degenerative joint disease – Inability of the patient to return to pre-injury levels of activity (e.g., work, sports) – Meniscus-related injuries – Neurovascular injury – Effusion, infection, swelling – Synovitis	No specific rates reported in the clinical literature for surgery-related complications during knee ligament reconstruction surgery.	**Overall: 90.5% (N=36/40), 39**		**Overall: 97.5% (N=39/40), 43**	None reported
		Foreign body (guide wire)	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Foreign body (granuloma)	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Inflammation	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Synovitis	5.0% (N=2/40), 2	5.0% (N=2/40), 2	
		Neuroma	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Dermatitis	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Post procedural inflammation	2.5% (N=1/40), 1	5.0% (N=2/40), 2	
		Necrosis	2.5% (N=1/40), 1	2.5% (N=1/40), 1	

Undesirable side effects, potential risks & adverse events as disclosed in the IFU	**Reported in State-of-the-art Literature**	**Reported for OrthoPure XT** *[pre-market clinical data and PMCF activities for isolated primary ACL reconstruction indication]*			**Reported in OrthoPure XT PMS (Complaints) data**
			2 years *[% of cohort affected (n), no. of events]*	**5 years** *[% of cohort affected (n), no. of events]*	
Surgery-related complications *(Continued)* e.g. – Complications associated with fixation hardware, including lack of isometry, and bone tunnels being too acute – Foreign body inflammation (including those in response to complications with fixation hardware including guide wires and fixation screws) – Complications requiring further surgical intervention (e.g., removal of fixation device) – Complications relating to the surgical procedure and anaesthesia, including, but not limited to infection, release of knee stiffness, pain, and haematoma	*Per previous page*	Oedema (swelling)	2.5% (N=1/40), 1	2.5% (N=1/40), 1	*Per previous page*
		Pyrexia (fever)	12.5% (N=5/40), 5	12.5% (N=5/40), 5	
		Swelling	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Suture-related complication	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Arthralgia (pain)	10.0% (N=4/40), 4	12.5% (N=5/40), 6	
		Joint effusion	22.5% (N=9/40), 10	22.5% (N=9/40), 10	
		Joint swelling	5.0% (N=2/40), 4	5.0% (N=2/40), 4	
		Synovial cyst	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Tendonitis	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Rash	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Haematoma	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Osteomyelitis (bone infection)	2.5% (N=1/40), 1	2.5% (N=1/40), 1	

Undesirable side effects, potential risks & adverse events as disclosed in the IFU	**Reported in State-of-the-art Literature**	**Reported for OrthoPure XT** *[pre-market clinical data and PMCF activities for isolated primary ACL reconstruction indication]*			**Reported in OrthoPure XT PMS (Complaints) data**
		2 years *[% of cohort affected (n), no. of events]*		**5 years** *[% of cohort affected (n), no. of events]*	
Device-related complications e.g. – Residual laxity and symptoms of instability – Pain and/or numbness – Knee laxity – Limited knee range of motion – Kneeling discomfort – Osteoarthritis/degenerative joint disease – Inability of the patient to return to pre-injury levels of activity (e.g., work, sports) – Effusion, infection, swelling	No specific rates reported in the clinical literature for device-related complications during knee ligament reconstruction surgery.	**Overall: 37.5% (N=15/40), 17**		**Overall: 55.0% (N=22/40), 24**	None reported
		Post- procedural inflammation	2.5% (N=1/40), 1	5.0% (N=2/40), 2	
		Ligament operation	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Ligament rupture	7.5% (N=3/40), 3	12.5% (N=5/40), 5	
		Pyrexia (fever)	10.0% (N=4/40), 4	10.0% (N=4/40), 4	
		Arthralgia (pain)	5.0% (N=2/40), 2	12.5% (N=5/40), 5	
		Joint effusion	5.0% (N=2/40), 2	5.0% (N=2/40), 2	
		Joint swelling	2.5% (N=1/40), 3	2.5% (N=1/40), 3	
		Synovitis	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Oedema peripheral	0% (N=0/40), 0	2.5% (N=1/40), 1	
Infections	Weighted average rate for infection determined from state-of-the-art literature: 0%	**Overall: 2.5% (N=1/40), 1**		**Overall: 2.5% (N=1/40), 1**	None reported
		Osteomyelitis (bone infection)	2.5% (N=1/40), 1	2.5% (N=1/40), 1	

Undesirable side effects, potential risks & adverse events as disclosed in the IFU	**Reported in State-of-the-art Literature**	**Reported for OrthoPure XT** *[pre-market clinical data and PMCF activities for isolated primary ACL reconstruction indication]*			**Reported in OrthoPure XT PMS (Complaints) data**
		2 years *[% of cohort affected (n), no. of events]*		**5 years** *[% of cohort affected (n), no. of events]*	
Venous Thromboembolism	No specific rates reported in the clinical literature for venous thromboembolism as a result of knee ligament reconstruction surgery.	**0% (N=0/40), 0**		**0% (N=0/40), 0**	None reported
Reoperation e.g. – Meniscus-related injuries – Residual laxity and symptoms of instability – Complications requiring further surgical intervention (e.g., removal of fixation device	Overall weighted average rate for re-operation following ACL reconstruction determined from state-of-the-art literature: 10.2%	**Overall: 22.5% (N=9/40), 9**		**Overall: 22.5% (N=9/40), 9**	None reported
		Post procedural inflammation	2.5% (N=1/40), 1	5.0% (N=2/40), 2	
		Ligament operation	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Ligament rupture	7.5% (N=3/40), 3	12.5% (N=5/40), 5	
		Synovitis	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Inflammation	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Foreign body reaction (granuloma)	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Neuroma	2.5% (N=1/40), 1	2.5% (N=1/40), 1	
		Ligament injury	0% (N=0/40), 0	2.5% (N=1/40), 1	

4.2. Warnings and precautions

The warnings and precautions as documented in the Instructions for Use are:

- The device is intended for use by Orthopaedic surgeons.
- This device has been designed for single use only. Reuse, reprocessing, resterilisation or repackaging may compromise the structural integrity and/or essential material and design characteristics that are critical to the overall performance of the device and may lead to device failure which may result in injury or illness of the patient.
- Reuse, reprocessing, resterilisation or repackaging may also create a risk of contamination of the device and/or cause patient infection or cross infection, including, but not limited to the transmission of infectious diseases from one patient to another.
- Contents supplied STERILE using gamma irradiation. Prior to use, carefully examine package and product to verify neither is damaged and that all seals are intact. Do not use if the package is damaged or has been unintentionally opened before use.
- Do not use after the "Use By" date specified on the package. Ensure that the device has been properly stored at ambient conditions (10-30 °C).
- Do not use the device if damaged prior to implantation as this may negatively impact the performance of the device.
- Do not let the device dry out as this may negatively impact the performance of the device.
- OrthoPure® XT is supplied in 4 sizes.
    - Size 5 is supplied as a single decellularised tendon.
    - Size 6 is supplied as a single decellularised tendon.
    - Size 8 is supplied as two single decellularised tendons which when used together are 8-9 mm in size. For **ACL reconstruction both tendons must be used** to ensure an appropriate biomechanical strength of the graft for this indication.
    - Size 10 is supplied as three single decellularised tendons. When all three tendons are used together, the graft is 9.5-11 mm in size. For **PCL reconstruction, all three tendons must be used** to ensure an appropriate biomechanical strength of the graft.
- OrthoPure® XT product formats may be used in the reconstruction of multiple knee ligament injuries as recommended, and in any combination. Do not implant more than seven decellularised tendons in a patient within a 24-hour period.
- Should a patient require implantation of more than seven decellularised tendons, additional tendons can be implanted after 7-days.
- The use of sutures for fixation is not recommended.
- The use of OrthoPure® XT in pregnant and breastfeeding women has not been studied.

4.3. Other relevant aspects of safety

OrthoPure® XT is derived from pig tissue. The risk associated with disease transmission from the pig to the patient has been assessed, with the following aspects considered:

- Source animal species;
- Sourcing of animal tissue (including geographical origin);
- Nature of starting material used;
- Methods used to remove and/or inactivate viruses or transmissible agents as part of the manufacturing process;
- Quantities of animal starting material required to produce each device;
- Quantities of material of animal origin coming into contact with the patients and users;
- Route of administration.

Pigs are considered to be a non-TSE relevant species, and therefore the risk of TSE transmission from the animal to the patient is negated.

Two process reagents - acetone and peracetic acid - used during the manufacture of OrthoPure® XT have been shown to successfully inactivate a panel of representative model viruses. Terminal sterilisation using gamma irradiation also significantly contributes to assurance of viral safety.

The risk associated with disease transmission from the pig to the patient is at a safe and acceptable level, in line with applicable regulatory standards. This is ensured via control over the raw material supply and harvest, as well as controls in the manufacturing process. Regular reviews of zoonosis (cross species disease transmission) are performed as a preventative measure to ensure this risk profile is maintained.

OrthoPure XT is a permanent implant which is not intended to be removed from the patient once implanted.

OrthoPure XT is expected to have a functional lifetime of approximately 2 years. This is the time for which the device contributes to the stability of the knee joint. During this time the device is gradually remodelled and replace by the patient's own tissue. Following this time, further changes may occur to the remodelled ligament, but these are not substantial, and the majority of the ligament is expected to be the patient's own tissue.

It is acknowledged that remnants of the device material may remain within the patient's body for the lifetime of the patient. As such, the biological lifetime of the device could be up to 60 years.

There have been no field safety corrective actions (FSCA) associated with OrthoPure® XT.

5. Summary of clinical evaluation and post-market clinical follow-up (PMCF)

5.1. Summary of clinical data related to equivalent device, if applicable

Equivalence was not used in the clinical evaluation of OrthoPure® XT.

5.2. Summary of clinical data from conducted investigations of the device before the CE-marking, if applicable

OrthoPure® XT has been subject to one premarket clinical investigation. A summary of this investigation is provided in Table 4.

Table 4: OrthoPure® XT premarket clinical investigation TRG-A01-01 summary.

Study reference	TRG-A01-01
Study title	A Prospective, Non-comparative Clinical Investigation of a Novel Decellularised Porcine Xenograft (OrthoPure® XT) for Reconstruction of the Anterior Cruciate Ligament
Subject device name	OrthoPure® XT
Intended use of the device in the investigation	The reconstruction of damaged and ruptured intra-articular knee ligaments to restore knee function and stability.
Objectives of the study	**Primary objective** To assess the safety and performance of dCELL® ACL Scaffold (OrthoPure® XT) in its intended use in patients with a ruptured ACL. **Secondary objective** To assess patient's knee functional improvement following implantation with dCELL® ACL Scaffold (OrthoPure® XT).
Study design	A prospective, open arm, multicentre clinical investigation.
Study endpoints	**Primary endpoints:** • Improvement of knee stability as measured by the side-to side differences (SSD) in mm between the treated knee and the treated knee; • Clinical assessment of knee stability using Lachman and Pivot shift tests on the treated knee at screening and follow-up. • Safety and tolerability of OrthoPure® XT was assessed by recording all adverse events (AEs) and serious adverse events

Study endpoints *(continued)*	(SAEs) reported by subjects in the investigation. In addition, the need for re-intervention was recorded. **Secondary endpoints:** Ease of use of the study device was evaluated at implantation. The functional improvement in the knee was assessed by Patient Reported Outcome Measures (PROMs): • International Knee Documentation Committee (IKDC) score change from baseline; • Lysholm score change from baseline; Knee Osteoarthritis and Injury Outcome Score (KOOS) score change from baseline.
Inclusion/exclusion criteria	1. Male and female patients at 18-60 years old, inclusive. 2. Patients must have partial or complete tear of the ACL and require reconstruction of the ACL. 3. Passive flexion ≥ 120° and passive extension on the target knee is the same as the contralateral knee in the judgment of the Investigator. 4. Medial Collateral Ligament (MCL) injury grade 2 or less. 5. Osteoarthritis grade 2 or less on the Kellgren Lawrence scale. 6. Ability to communicate meaningfully with investigative staff, competence to give written informed consent; and willingness and ability to comply with entire study procedures including rehabilitation protocol.
Exclusion criteria	1. Treatment with any investigational drug or device within two months prior to Visit 1. 2. If female and of child-bearing potential must not have a positive pregnancy test at Visit 1 nor have a stated intention to become pregnant in the next 12 months. 3. Patients presenting with abnormal degenerative osteoarthritis of the joint [e.g. International Cartilage Repair Society (ICRS) Grade III or higher] as determined by the baseline MRI scan. 4. Patients must not have had previous ACL reconstruction on the target knee. 5. Patients must not have any other type of surgical procedure on the target knee in the previous three months prior to Visit 1. 6. Current ACL injury on contralateral knee. 7. Severe pain, swelling or redness at the surgery site within 24 hours prior to surgery. 8. Complete or partial Lateral Collateral Ligament (LCL) or Post Cruciate Ligament (PCL) tear on the target knee. 9. Meniscal repairs and tears requiring more than one third (1/3) removal on the target knee as determined during knee arthroscopy, in the judgment of the Investigator.

Exclusion criteria *(continued)*	10. Patients with severe articular cartilage defect (ICRS Grade III or higher) on the target knee as determined during knee arthroscopy. 11. Active systemic infection, or local infection at the surgery site. 12. Psychological disorder that would impair the patient's ability to answer the study questionnaires. 13. Body Mass Index (BMI) greater than 35 kg/m^2. 14. Patients using anticoagulants within 2 weeks prior to surgery. 15. Patients on current immuno-suppressive or radiation therapy or having received such therapies within six months of Visit 1. 16. Patients with diabetes or cardiovascular disease which precludes elective surgery. 17. Patients with documented renal disease or metabolic bone disease. 18. Patients with known allergy to porcine material or a religious objection to the use of implanted porcine material. 19. Patients with history of, or current drug and alcohol abuse. 20. Any condition which, in the judgment of the Investigator, would preclude adequate evaluation of OrthoPure® XT Scaffold's safety and performance.
Number of enrolled subjects	40 patients.
Study population	Patients who require reconstruction of primary ruptured anterior cruciate ligament of the knee.
Summary of study methods	**Methods and timing for assessing, recording and analysing variables** <u>Visit 1 – Screening, Day -30 to Day 0</u> All subjects identified for participation in the study and meeting inclusion/exclusion criteria will have the following conducted/recorded/assessed at the screening visit: • Informed Consent Process • Demographics, Past Medical History Physical Examination • Pregnancy test (female patients of childbearing potential only) • Knee X-ray (scheduled, if not done within 6 months prior to screening) • Knee MRI scheduled • Arthrometric Ligament Laxity test • Lachman test • Pivot shift test • IKDC • Lysholm Score • KOOS

Summary of study methods *(continued)*	• Recording of Medications Visit 2 – Surgery, Day 0 Eligibility criteria will be reviewed. If subject remains eligible, the subject will undergo ACL reconstruction procedure with dCELL® ACL Scaffold (OrthoPure® XT). Ease of use and placement of the dCELL® ACL Scaffold will be assessed (in order to ensure that surgeons do not find the device too difficult to use) and recorded in the CRF. Adverse events (intraoperative) will be recorded. A Sponsor's representative may be present during surgery. Visits 3 – Day 5 to 9 • Review Rehabilitation • Recording of Adverse Events • Recording of Change in Medications Visits 4 - 7 These visits will be conducted at 3 months (± 7 days), 6 months (± 14 days), 12 months (± 14 days), and 24 months (± 14 days) after surgery. The following will be recorded: • Knee X-ray at Visit 4 only (3 months) to assess position of the bone tunnels and fixation, and evidence of tunnel-widening and interference screws • Knee MRI • Arthrometric Ligament Laxity test • Lachman test • Pivot shift test • IKDC • Lysholm Score • KOOS • Review Rehabilitation (up to visit 5 at 6 months) • Recording of Adverse Events and the need for surgical re-intervention • Recording of Change in Medications **Statistical – Populations for Analysis** All subjects implanted with OrthoPure® XT and completing any follow up visit will be in the Safety Analysis Set (N=40). In addition, subjects who completed the study to the 24-month time point without any major protocol deviation, and whom complete primary endpoint data is available at baseline and 24-month timepoints will be in the Performance Analysis set (N=33). The primary and secondary endpoints will be analysed at two time points: 6 months (interim analysis) and 24 months (final analysis). An additional interim analysis may be performed if required by the Sponsor.

Summary of study methods *(continued)*	The sample size was sufficient to ensure that 35 subjects would reach the 24-month time point and ensure sufficient statistical power for the pre-clinical part of the study.
Summary of results	**Safety** No atypical trends in adverse events were identified for the OrthoPure XT device, and as such it was concluded that no new or unexpected risks were identified from this data. During the 24-month follow-up study period, 4 out of 40 subjects (10.0%) had suffered an ACL rupture or required revision surgery. The rupture was traumatic for one subject, atraumatic for one subject (rupture due to extensive rehabilitation out of the study protocol). One subject suffered chronic instability and underwent revision ACL reconstruction, and one subject underwent revision ACL reconstruction outside of the study. Evidence of unfavourable surgical technique and notch impingement were identified via review of MRI images for these subjects, and is the most likely root cause. The reconstruction failure rate reported within the study at the 2-year time-point is therefore 10.0% (4/40).Two of the 17 reported SAEs were reported to be device related by the study investigators. One (post-procedural inflammation) was resolved by removal of the fixation device (screw). One (ligament operation) was resolved by revision of the ACL reconstruction outside of the investigational study. Fifteen adverse events were reported to be device related by the study investigators, of which two (post-procedural inflammation and ligament rupture) led to SAEs. Five SAEs (granuloma, synovitis, and inflammation) were resolved by the removal of the bioresorbable fixation screw. Pre-clinical data generated for OrthoPure XT (large animal study) supports the use of the device with bioresorbable fixation screws. Data shows that the device does not interfere with the biosorption process, and that the biological response to the bioresorbable screw is comparable when used with the OrthoPure XT device vs. allograft tissue. The potential for a xenograft response was assessed, involving a review of both recurrent swelling and effusion and recurrent episodes of fever beyond the 6 month time point. A review of the safety data set was performed for all data, and included both

Summary of results *(continued)*	device related events and non-device related events. Based on these criteria no xenograft response was identified. Other safety events identified were typical for ACL reconstruction with allograft and autograft in terms of type, frequency and severity. These outcomes met the clinically relevant expectation identified in the Clinical Data Protocol. **Performance** Statistical equivalence between the anterior displacement (in mm) of the operated and non-operated knees (Side-to-Side difference, SSD) was demonstrated at the 24-month time point ($p<0.001$). The level of residual laxity for the cohort as measured by arthrometer assessment of SSD (33.3%) were typical following ACL reconstruction (11-43%), and no adverse trends were identified. Statistical and clinically relevant improvements from baseline were demonstrated for the Lachman ($p<0.001$) and Pivot-Shift ($p<0.001$) tests at the 24-month time point. Lachman test showed the level of residual laxity for the study cohort (36.4%, n=12/33) to be typical following ACL reconstruction (≤48%). 84.8% of the cohort (n=28/33) showed an improvement from baseline at the 24-month time point. No adverse trends were identified. Pivot Shift Test showed the level of residual laxity for the study cohort (24.2%, n=8/33) to be typical following ACL reconstruction (≤73%). 63.6% of the cohort (n=21/33) showed an improvement from baseline at the 24-month time point. No adverse trends in data were identified. Statistical and clinically relevant improvements from baseline have been shown for the International Knee Documentation Committee (IKDC) score ($p<0.001$), Lysholm score ($p<0.001$), and all sub-sections of the Knee Injury and Osteoarthritis Outcome Score (KOOS) (all $p<0.001$) at 24-months follow-up. The average IKDC score for the study cohort was 91.0 (± 9.3) at 24-month follow up, which is typical following primary ACL reconstruction (≥55). 100% of the cohort (n=33/33) showed an improvement from baseline at the 24-month time point. No adverse trends in the data were identified.

Summary of results *(continued)*	The average Lysholm score for the study cohort was 95.1 (± 7.4), which is typical following primary ACL reconstruction (≥65). 93.9% of the cohort (n=31/33) showed an improvement form baseline. No adverse trends in the data were identified. Average KOOS scores for the study cohort were as follows at 24-month follow-up, which is typical following primary ACL reconstruction: • Symptoms: 96.5 (± 3.9), expectation ≥ 80 • Pain: 97.5 (± 4.2), expectation ≥ 75 • Function in daily living: 99.2 (± 2.9), expectation ≥ 85 • Function in sport and recreation: 92.7 (± 11.3), expectation ≥ 65 • Knee related quality of life: 80.9 (± 17.3), expectation ≥ 60 An improvement from baseline was shown in 84.8-97% of the cohort. No adverse trends in the data were identified in any of the KOOS score sub-groups. Magnetic Resonance Imaging (MRI) was included in the clinical study as a secondary measure of efficacy, used to assess graft status (e.g. to identify ruptures and ligamentisation / remodelling). No atypical trends were observed in the MRI and X-ray analysis, which included a review of changes in internal derangement, evidence of tunnel widening, evidence of graft failure, evidence of ligamentisation, fixation and bone tunnel positioning. Since biopsies cannot be taken from study participants post-implantation to directly evaluate the biological state of the graft, MRI serves as a valuable alternative for monitoring its condition over time. However, to fully understand the graft's performance and the ligamentisation process, MRI findings cannot be used in isolation and have therefore been interpreted alongside other clinical endpoints, to ensure a more comprehensive evaluation of the safety and performance of OrthoPure XT. Histopathologic assessment of explanted device material was performed in cases where explants were available (n = 4). Notably, ligamentisation was observed in two subjects (706 and 802) whose explants were taken at approximately 2- and 3-years post-implantation, respectively. However, a review of MRI assessments for these same patients at their 24-month follow-

Summary of results *(continued)*	up showed they were graded as zero for ligamentisation. This discrepancy supports the hypothesis that MRI alone is not a reliable indicator of successful graft remodelling. Histopathologic assessment of explants taken at 7- and 9-months post implantation did not indicate any evidence of ligamentisation (n = 2, subjects 805 and 705 respectively), however, this is to be expected during the early remodelling phase with ligamentisation occurring between 10 months to 2 years post implantation. New onset of meniscal tears was identified in 1/33 (3.0%) of subjects, and new onset of cartilage damage was found in 1/33 (3.0%) of subjects at the 24-month time point. No loose bodies were identified. It should be noted that one subject was excluded from the performance cohort due to a significant protocol deviation. One subject's ACL was reconstructed using a single decellularised tendon. The Size 8 device, indicated for ACL reconstruction, is comprised of two decellularised tendons, both of which must be used. This risk is already considered within the risk management file and is considered within the device labelling, therefore this is not a new risk. It is worth nothing that ACL reconstruction was still successful in this subject. Assessment of the ease of use of the device was reported as 'excellent' or 'good' in all cases. No specific criteria apply for this assessment; however, this data demonstrates that the device's physical format is fit for its intended use, and that no changes to the design format are needed. **Conclusion** The 24-month clinical safety and performance data for the OrthoPure XT device meet the clinically relevant expectations that have been determined in the Clinical Data Protocol based on clinical expectations for primary ACL reconstruction. These outcomes demonstrate that the device is safe and performs as intended. No new or unexpected risks have been identified during use of the device throughout its functional lifetime.
Study limitations	None

Device deficiencies and device replacements	**Device Deficiencies** One device deficiency was reported. This deficiency was not associated to an AE and might not have led to a SAE. The type of deficiency was reported as 'durability' and 'performance'. The description of the device deficiency was: 'small subject, narrow intercondylar space - use of one implant string instead of two'. **Device Replacements** In the pre-market phase 4 out of 40 subjects (10.0%) had suffered an ACL rupture or required revision surgery.

5.3. Summary of clinical data from other sources, if applicable

Anterior cruciate ligament reconstruction

The overall clinical experience with OrthoPure® XT for ACL reconstruction is documented in the current Clinical Evaluation Report.

The study protocol of the premarket study described in section 5.2, *(study reference TRG-A01-01)* was amended to specify that pre-market follow-up would be up to 2 years, with long-term data collected out to 5 years. The follow-up of patients enrolled in this study forms part of the proactive post market surveillance (PMS) activities for OrthoPure® XT for ACL reconstruction. The methodology used for the long-term data collection and analysis of data during the post-market phase (at years 3, 4 and 5), reflects that of the study protocol summarised in section 5.2.

An executive summary of the clinical data for the OrthoPure® XT device when used for primary ACL reconstruction for subjects who have been followed out to **5 years** (60 months) is provided in the following sections.

Device Safety

No atypical trends in adverse events have been identified for the OrthoPure® XT device. The pattern of SAEs and AEs are typical to post-operative reactions observed following ACL reconstruction. As such it can be concluded that no new or unexpected risks have been identified from the data.

Device Performance

Statistical equivalence between the anterior displacement (in mm) of the operated and non-operated knees (Side-to-Side difference, SSD) was demonstrated at the 5-year time point ($p<0.05$). The level of residual laxity for the cohort as measured by arthrometer assessment of SSD (33.3%), were typical following ACL reconstruction (11-43%), and no adverse trends were identified.

Statistical and clinically relevant improvements from baseline were demonstrated for the Lachman ($p<0.001$) and Pivot-Shift ($p<0.001$) tests at the 5-year time point.

Lachman test showed the level of residual laxity for the study cohort (33.3%, n=6/18) to be typical following ACL reconstruction (≤48%). 94.4% of the cohort (n=17/18) showed a clinically relevant improvement from baseline at the 5-year time point. No adverse trends were identified.

Pivot Shift Test showed the level of residual laxity for the study cohort (11.1%, n=2/18) to be typical following ACL reconstruction (≤73%). 72.2% of the cohort (n=13/18) showed a clinically relevant improvement from baseline at the 5-year time point. No adverse trends in data were identified.

Statistical and clinically relevant improvements from baseline have been shown for the International Knee Documentation Committee (IKDC) score ($p<0.001$), Lysholm score ($p<0.001$), and all sub-sections of the Knee Injury and Osteoarthritis Outcome Score (KOOS) (all $p<0.001$) at 5-year follow-up.

The average IKDC score for the study cohort was 93 (± 8) at 5-year follow up, which is typical following primary ACL reconstruction (≥55). 94.4% of the cohort (n=17/18) showed a clinically relevant improvement from baseline at the 5-year time point. No adverse trends in the data were identified.

The average Lysholm score for the study cohort was 95 (± 7), which is typical following primary ACL reconstruction (≥65). 94.4% of the cohort (n=17/18) showed a clinically relevant improvement form baseline. No adverse trends in the data were identified.

Average KOOS scores for the study cohort were as follows at 5-year follow-up, which is typical following primary ACL reconstruction:

- Symptoms: 93 (± 8), expectation ≥ 80
- Pain: 97 (± 5), expectation ≥ 75
- Function in daily living: 98 (± 6), expectation ≥ 85
- Function in sport and recreation: 89 (± 13), expectation ≥ 65
- Knee related quality of life: 84 (± 16), expectation ≥ 60

A clinically relevant improvement from baseline was shown in 61.1-94.4% of the cohort. No adverse trends in the data were identified in any of the KOOS score sub-groups.

Reconstruction Failure

During the 3–5-year post-market follow-up study period, a further 3 out of 40 subjects (7.5%) have suffered an ACL rupture or required revision surgery. The rupture was traumatic for 1 subject. Evidence of unfavourable surgical technique was identified for 1 subject, and there was no obvious cause for one subject. Therefore, the cumulative revision rate reported within the study, inclusive of pre-market and post-market phases, is 17.5% (7/40). Overall, issues likely to have led to the re-rupture of the graft were identified in 15% (6/40) of subjects (trauma, excessive wear, unfavourable surgical techniques and impingement of the graft). No obvious case was identified for 2.5% (1/40) of subjects, and therefore this may have been a

device failure. The rate reported is not atypical following ACL reconstruction using the current standard of care (23 %) and no emerging or adverse trends have been identified.

Conclusion

The 5-year clinical safety and performance data for the OrthoPure XT device meet the clinically relevant expectations that have been determined in the Clinical Data Protocol based on clinical expectations for primary ACL reconstruction. These outcomes demonstrate that the device is safe and performs as intended. No new or unexpected risks have been identified following long-term use of the device, beyond the functional lifetime.

Multi-ligament reconstruction of the knee

It is important to note that knee dislocations, resulting in multi-ligament damage, account for less than 0.02% of all orthopaedic injuries which creates a challenge for conducting clinical studies to investigate these types of injuries [5]. Due to the variable nature of the injury itself, variability in associated injuries (e.g. fractures, vascular damage, nerve damage, other trauma), and variable mechanisms of injury, variable treatment patterns etc., it is near impossible to perform a true comparative study with a level of control and confidence [5].

The overall clinical experience with OrthoPure® XT for multi-ligament reconstruction of the knee is documented in the current Clinical Evaluation Report.

In summary, clinical data have demonstrated the following, with respect to device performance:

- Good functional outcomes are achieved when using the OrthoPure® XT device for reconstruction of isolated knee ligament injuries (primary ACL reconstruction), specifically:
    - Significant improvements in joint laxity achieved in comparison to pre- surgery levels, and levels of residual joint laxity within the population exceed expectations identified for the current gold standard of care for the target ligament assessed, as demonstrated by Lachman and Pivot Shift Tests.
    - Statistically equivalent levels of anterior displacement (mm) achieved between the operated and non-operated knee, and levels of residual joint laxity (indicated by a SSD[a] of >3mm) within the population exceed expectations identified for the current gold standard of care for the target ligament assessed, as demonstrated by arthrometer assessment of SSD.
      [a] SSD denotes side to side difference in mm between the anterior displacement in the operated knee vs the non-operated knee.
    - Significant improvement in the perceived function of the knee by the patient and reduction in pain and symptoms, with mean scores exceeding expectations for the current gold standard of care for the target ligament assessed, as demonstrated by IKDC[b], Lysholm, and KOOS[c] scores.
      [b] IKDC denotes International Knee Documentation Committee score.

[c] *KOOS denotes Knee Injury and Osteoarthritis Outcome score.*

- Clinical outcomes established for isolated reconstruction of the ACL fall within the expectations for clinical outcomes following multi-ligament knee injury (MLKI), indicating that the device is not expected to introduce additional residual laxity or further complications with respect to knee function when used during treatment of MLKI.
- 'Ease of use' data for the device has shown that the device's physical format is fit for its intended use, and that no changes to the design format are needed

It is clear from the clinical data reviewed that the OrthoPure® XT device serves as a suitable alternative to human tendon autograft and allografts (autograft being the current gold standard of care for ACL reconstruction) for knee ligament reconstruction.

Given the similarities between reconstruction of the ACL and reconstruction of the knee ligaments compromised during MLKI (i.e. similar reconstruction technique, same contact sites & tissues, same fixation methods, same or lower expectations with respect to functional outcomes), the device material can therefore be considered appropriate for use in ligament reconstruction where the use of autograft or allograft would be considered.

It can be concluded therefore that the OrthoPure® XT device is highly likely to improve levels of knee function sufficiently to support a return to daily levels of activity.

The planned post-market clinical follow-up study involving OrthoPure® XT for multi-ligament reconstruction of the knee has commenced, however, to date no clinical data has been generated from this study.

Clinical data from medical device registries

OrthoPure® XT has been added to the UK National Ligament Registry (NLR). To date, no data pertaining to the use of OrthoPure® XT has been entered into the NLR.

5.4. An overall summary of the clinical performance and safety

OrthoPure® XT is a class III implantable medical device with a positive benefit-risk profile.

OrthoPure® XT is integrated by the body following implantation. The decellularised tissue material provides an 'extracellular collagen matrix' (ECM), which facilitates a remodelling process, whereby the host cells infiltrate the scaffold post implantation. The remodelling process occurs during rehabilitation.

Analysis of clinical data on OrthoPure® XT has been conducted. This information demonstrates that OrthoPure® XT, when used under the conditions and for the purposes as intended, will not compromise the clinical condition or safety of patients, or the safety and health of users. Based on the analysis of the clinical data, the intended clinical benefit to patients is to help restore knee stability and normal knee function.

Benefits of utilizing the subject device are substantiated via evidence presented in the Clinical Evaluation Reports that assess its ability to achieve its purpose as claimed.

The pre-market and post-market clinical investigations showed that OrthoPure XT was safe when used as intended over the functional lifetime of the device and beyond. Clinical safety data available for the OrthoPure XT device demonstrates the following:

- When used for isolated ligament reconstruction (primary ACL reconstruction), the safety profile for the OrthoPure XT device is in line with expectations identified for the current gold standard of care for the target ligament
- When used for isolated ligament reconstruction (primary ACL reconstruction), the OrthoPure XT device does not introduce any new or unexpected risks
- The OrthoPure XT device is considered safe for use in knee ligament reconstruction

It can be concluded therefore that the OrthoPure XT device is safe for use in knee ligament reconstruction.

Clinical data have demonstrated the following, with respect to device performance:

- Good functional outcomes are achieved when using the OrthoPure XT device for reconstruction of isolated knee ligament injuries (primary ACL reconstruction), specifically:
    - Significant improvement in the perceived function of the knee by the patient and reduction in pain and symptoms, with mean scores exceeding expectations for the current gold standard of care for the target ligament assessed, as demonstrated by IKDC, Lysholm, and KOOS scores. In particular, post-operative IKDC and KOOS scores obtained from patients implanted with OrthoPure XT were comparable or better than in patients treated with autografts.
    - Significant improvements in joint laxity achieved in comparison to pre-surgery levels, and levels of residual joint laxity within the population exceed expectations identified for the current gold standard of care for the target ligament assessed, as demonstrated by Lachman and Pivot Shift Tests
    - Statistically equivalent levels of anterior displacement (mm) achieved between the operated and non-operated knee, and levels of residual joint laxity (indicated by a SSD movement of >3mm) within the population exceed expectations identified for the current gold standard of care for the target ligament assessed, as demonstrated by arthrometer assessment of SSD
    - Levels of residual joint laxity within the population exceed expectations identified for the current gold standard of care, as demonstrated by SSD, Lachman and Pivot Shift Tests
- Clinical outcomes established for isolated reconstruction of the ACL fall within the expectations for clinical outcomes following MLKI, indicating that the device is not expected to introduce additional residual laxity or further complications with respect to knee function when used during treatment of MLKI
- 'Ease of use' data for the device has shown that the device's physical format is fit for its intended use, and that no changes to the design format are needed

It is clear from the clinical data that the OrthoPure XT device serves as a suitable alternative to human tendon autograft and allografts for ligament reconstruction. It can be concluded

therefore that the OrthoPure XT device is highly likely to improve levels of knee function sufficiently to support a return to daily levels of activity for all indications specified.

Residual risks associated with the device are those inherent to the nature of the device, i.e. permanent, sterile, animal derived implant. Whilst these risks have been reduced as far as possible to a tolerable level during the design process, they can never be fully eliminated due to the severity of harm associated with these risks.

The long terms risks identified for the use of the OrthoPure XT device for ACL reconstruction are autologous with those expected for the current gold standard of care.

Information collected through Tissue Regenix' Post Market Surveillance (PMS) activities assess risks. Results of the risk analysis demonstrate that use of the device as intended is unlikely to adversely affect the health or safety of the patient or user. The risks associated with the device, including potential undesirable adverse effects constitute acceptable risks when weighed against the benefits to the patient.

5.5. Ongoing or planned post-market clinical follow-up

Post market clinical follow up (PMCF) for OrthoPure® XT is covered by the OrthoPure® XT Post Market Plan, which documents the methods and procedures for proactively collecting and evaluating clinical data for the device.

The following general methods and procedures of PMCF are currently being applied:

- PMCF studies, specifically:
  - ACL indication PMCF study. Pre-market study cohort followed out to 5 years (study complete and results included herein)
  - Multi-ligament indication PMCF multi-centre case series study, followed out to 2 years (study in progress; no data current available)
  - Multi-centre post-market registry collecting performance and safety data for subjects treated with the OrthoPure XT device for isolated primary and revision ACL reconstruction. Data to be collected via a registry controlled by the manufacturer
- Complaints & Feedback, including AE and SAE Events Reporting
- Explant analysis
- Market/customer inputs (Customer feedback surveys)
- Review of scientific literature
- Review of registry data
- Review of market surveillance data by regulatory authorities (Review of regulatory vigilance databases)
- Review of market publications by regulatory authorities (Review of information generated by regulatory bodies, including updates to international standards, industry guidance and best practices)

- Annual product review of production and post-production data (device distribution tracking, finished products and product quality information, audits and inspection data)

To date, no emerging risks, complications or unexpected device failures have been detected.

6. Possible diagnostic or therapeutic alternatives

A variety of graft sources, such as autografts, allografts, and commercially available synthetic grafts (see devices summarised in Table 5) are available for treatment of knee ligament injuries.

An overview of commercially available devices that may be used for MLKI and ACL reconstruction is provided in Table 5.

Table 5: Commercially available devices that may be used for MLKI and ACL reconstruction

Device name (manufacturer)	Type	Key similarities with OrthoPure® XT	Key differences to OrthoPure® XT
Z-Lig® (Aperion Biologics Inc.)	Porcine Xenograft	• Intended use (ligament reconstruction, specifically indicated for ACL reconstruction). • Device material ('processed' porcine ligament xenograft). • Sterile device, single use. • Duration of use (permanent implant). • Device placement/body contact (bone/tissue). • Comparable biomechanical strength, with Z-Lig® averaging much lower (~1900N approximation) than the equivalent size of OrthoPure® XT (Size 8: 3359N ± 394N (mean ± SD)). • Provides biomechanical support, knee stabilisation and functionality to the patient immediately upon implantation. • Acts as a scaffold for gradual host cell re-population and remodelling.	• Z-Lig® is a bone-tendon-bone graft, whereas OrthoPure® XT is a soft tissue graft, therefore the specific fixation methods and devices used will differ. As both types of grafts (and their associated fixation devices) are widely used for ligament reconstruction with good clinical outcomes, the potential variance in clinical safety and performance data is expected to be minimal. • Z-Lig® requires specialist storage at -80 °C. • Z-Lig® is indicated for revision ACL reconstruction, or primary ACL reconstruction where multi-ligament injuries are present. • Z-Lig® and OrthoPure® XT undergo a processing treatment to render the porcine tissue safe for implantation into humans. The process applied to Z-Lig® differs in comparison to the dCELL® process used for OrthoPure® XT. The two devices will therefore likely differ in their composition, for example, differing concentration of residual cellular materials and processing reagents, differing effects on the tissue structure, differing sterilisation techniques. Each of these considerations has the potential to influence the expected safety and performance of the device.

Device name (manufacturer)	Type	Key similarities with OrthoPure® XT	Key differences to OrthoPure® XT
LARS™ System, (Corin group)	Synthetic (polyethylene terephthalate (PET)) graft	• Indication (acute ACL injuries (with caution), multi-ligament injuries). • Available in a range of sizes (diameters) to suit the intended use (4-9.5mm). • Available in a range of strengths (the 8mm LARS™ product (ACL-100) has a strength of 3000N; size 8 (8mm) OrthoPure™ XT has a strength of 3359N ± 394N (mean ± SD)). • Sterile, single use device. • No specialist storage requirements.	• Although host cells may infiltrate the structure of LARS™, the device itself will not undergo remodelling, compared to OrthoPure® XT. As such the LARS system will need to retain its functional biomechanical strength for the lifetime of the device. The device does not have the elongation properties of biological materials. This will differentiate the long-term safety and performance profiles of the two devices. • LARS™ requires the presence of viable ligament tissue remnants to be used for reconstruction, otherwise it is used for augmentation or reinforcement alongside autograft/allografts. • LARS™ is also indicated for augmentation and reinforcement. • LARS™ requires specialist accessories.
JewelACL™ (Neoligaments)	Synthetic (polyethylene terephthalate (PET)) graft	• Indication (ligament reconstruction, specifically ACL reconstruction is listed for JewelACL™) • Biomechanical strength (7mm diameter JewelACL™ ~1200N, comparable indication to size 8 OrthoPure® XT, having a strength of 3359N ± 394N (mean ± SD)) • Sterile, single use device	• Whilst host cells may infiltrate the polyester structure of the device, it will not undergo remodelling, compared to OrthoPure® XT. As such it will need to retain its functional biomechanical strength for the lifetime of the device. The device does not have the elongation properties of biological materials. This will differentiate the long-term safety and performance profiles of the two devices. • The JewelACL™ device requires specialist accessories. • JewelACL™ can be used to reconstruct or reinforce the ligament alongside another tissue graft.

Device name (manufacturer)	Type	Key similarities with OrthoPure® XT	Key differences to OrthoPure® XT
JewelACL™ (Neoligaments) *(continued)*	*As above*	*As above*	• JewelACL™ does not go through a remodelling phase which, the manufacturer states, facilitates early mobilisation and rehabilitation.
Ligastic® (Orthomed)	Synthetic (polyethylene terephthalate (PET)) graft	•The product is available in multiple product variations and can be used for reconstruction or reinforcement of the ACL, posterior cruciate ligament (PCL), medial collateral ligament (MCL) and lateral collateral ligament (LCL). •Sterile, single use device	• Whilst host cells may infiltrate the polyester structure of the device, it will not undergo remodelling, compared to OrthoPure® XT. As such will need to retain its functional biomechanical strength for the lifetime of the device. The device does not have the elongation properties of biological materials. This will differentiate the long-term safety and performance profiles of the two devices.

ACL reconstruction

ACL reconstruction is currently regarded as the standard treatment for ACL injury. ACL injury is also likely to result in damage of other constructs within the knee, such as the meniscus, which are often repaired concurrently with reconstruction of the ACL. Most orthopaedic surgeons agree that the ruptured ACL should be treated with reconstructive surgery, particularly for athletes considering returning to pivoting sports [6], however, no consensus exists about the optimum technique.

A variety of graft sources, such as autografts, allografts, and synthetic grafts have been used for ACL reconstruction [7].

Based on the information reviewed, reconstruction with an autograft is the preferred technique for primary ACL reconstruction (96-98%). The choice of graft material for ACL reconstruction remains controversial [13]. The majority of primary ACL reconstruction procedures are performed with one of the following graft types, combined with various fixation techniques [6, 7, 8, 9, 10]:

- Soft tissue graft (e.g. hamstring tendon, semitendinosus and/or gracilis)
- Bone-patellar tendon-bone ('BPTB' or 'BTB') graft

ACL reconstruction with either patellar tendon or semitendinosus tendon autografts are standard procedures [16, 18]. Studies have shown these grafts to be safe with good clinically functional results, and without major differences [8, 9, 11], however, debate about which graft provides the best long-term results is still ongoing [6, 10].

There is opinion within the literature that reconstruction with a BTB produces a more stable knee and is considered to provide good knee stability and the option to return to high-level (elite) sports [10, 11]. Donor site morbidity is a problem for both graft types, however it causes particular problems with elevated kneeling and anterior pain following harvest of the BTB graft [8, 9, 10, 11].

During the past decade, there has been a shift from BTB as the most common graft choice in favour of a hamstring graft as they are perceived to have less donor site morbidity than BTB grafts, with good clinical outcomes [6, 11].

With reference to the UK ACL registry (2020 report), hamstring tendon autograft in the form of a double semitendinosus and gracilis graft was the most commonly used autograft (79%) for ACL reconstructions, followed by semitendinosus alone (11%) and patellar tendon (9%).

The graft sources used for the majority of revision ACL reconstruction are the same as those for primary ACL reconstruction, namely autograft and allograft tissue. From the literature reviewed, the use of autografts is favoured for revision ACL reconstruction, with the use of hamstring soft tissue grafts and bone-tendon-bone grafts preferred. However, the use of allografts is also prevalent for revision ACL surgery, which is likely dictated by the availability, or lack thereof, of suitable autograft material, particularly if the patient's index (primary ACL reconstruction) procedure was performed using an autograft.

Complications and risks associated with use of autografts

Risks specific to the use of autograft tissues are associated with harvest of the graft from the patient, and subsequent donor site morbidity. These risks include, but are not limited to [7]:

- **For BTB grafts:**
  - Patellar fracture
  - Long-term kneeling pain
  - Potential increase in patellofemoral pain
  - Persistent patellar weakness or rupture
- **For soft tissue grafts:**
  - Potential muscle weakness at the harvest site
  - Slower healing of the graft attachment site
  - Saphenous vein trauma
  - Long-term knee flexor strength deficit

Complications and risks associated with the use of allografts

Allograft (human donor tissue) is less widely used in Europe for primary ACL reconstruction, despite strong evidence to support the use of 'appropriately processed' allografts.

There are many variables discussed with respect to the expected clinical performance of allograft tissues, including tissue quality, procurement, processing, storage and sterilisation. There is a potential trend in the literature towards higher failure rates for allograft in comparison to autograft.

Risks associated with allograft tissues include viral transmission from the donor, and bacterial infection where allografts have not been terminally sterilised (aseptically processed). Whilst the risks associated with viral transmission are low (1 in 1.6 million for HIV [12] and 1 in 421,000 for hepatitis C [13]), the potential impact of infection for the patient could be life changing.

There is evidence within the literature that the application of irradiation to allograft tissue results in a poorer clinical performance and increased failure rates (up to 33% reported). The effects of irradiation on tissue grafts have also been reported to be dose dependent, with higher doses resulting in worse clinical results.

The benefit of terminal sterilisation via irradiation is that it removes the risk of bacterial infection from the graft and has the potential to kill viruses. However, in order to eradicate HIV, doses in excess of 5 Mrad (50kGy) may be needed[12]. As such, the risk-benefit profile associated with irradiated allografts is heavily debated within the literature.

Multi-ligament reconstruction of the knee

Multi-ligament knee injuries (MLKI) are complex and infrequent injuries, which present a hugely complex clinical problem to individual clinicians who may not be used to dealing with such injuries routinely. The potential morbidity of this injury is significant, with instability and pain being reported many years after the initial injury [14], therefore these injuries can be life changing for patients.

Various treatments for MLKI have been reported in the literature with no consensus to the most appropriate form of universal treatment [15, 16, 17].

Given the complexity of the clinical condition, the specific individual circumstances of each patient should be considered, and personalised management of the injury decided upon between the patient and the surgeon [17]. The individual treatment protocol is heavily influenced by the injury pattern and associated injuries that the patient has sustained.

Treatment options to consider vary from non-operative treatment, (such as limb immobilisation, casting, or external fixation), through to surgical repair or reconstruction of the damaged ligaments [5].

Topics of continued debate within the literature relating to treatment include:

- Non-operative vs. surgical treatment
- Ligament repair vs. ligament reconstruction
- Early vs. delayed surgical treatment
- Single vs. phased surgical treatment
- Autograft vs allograft for surgical reconstruction

Graft choice for surgical reconstruction

While there is an expanse of information reported in the literature supporting the use of autograft for ACL reconstruction, these injuries frequently occur in isolation with minimal concomitant or associated injuries meaning that suitable tissue is available to harvest for this purpose.

In comparison, patients suffering from MLKI are a very different patient population. The use of autograft for MLKI is limited by the following factors [14]:

- The integrity of tissue remaining (and therefore available for use as an autograft) may be compromised by the injury.
- Consideration to the extent of injury suffered by these patients – surgeons are often reluctant to add further damage by harvesting tissue.
- The volume of tissue needed for full treatment of the injury leaves a surgeon with minimal options.

Allograft tissue is a popular option for MLKI as it negates concerns associated with additional harm to the patient and tissue availability, and also reduces operating time as the need for

graft harvest is negated. However, use of this material also comes with concerns and considerations such as:

- Sterility of the tissue
- Potential for pathogen transmission from donor to patient
- Tissue processing and the potential impact on structural integrity
- Tissue quality and consistency
- Cost
- Lack of availability in some countries and centres

Given the variability of the MLKI clinical condition, and variability within the literature with respect to treatment (reconstruction, repair, non-operative, allograft, autograft etc.) it is impossible to differentiate clinical outcomes associated with graft type alone.

Synthetic grafts are also seen as a reliable option where barriers exist to the use of alternatives[18, 19]. However, there may be limitations associated with their intended use that prevent their use in some instances, for example, LARS™ can only be used where sufficient native tissue remains [19].

Graft Remodelling & Ligamentisation

The expected biological response to the use of a tissue graft for ligament reconstruction is that the graft is remodelled by the body. Graft remodelling or 'ligamentisation' is the process by which a biological graft used in ligament reconstruction, (e.g. ACL reconstruction), undergoes transformation from a tendon, or other tissue, to a structure that mimics the function of the native ligament. These processes include changes in cellularity, vascularity and extracellular matrix to transform graft characteristics into the properties of the intact ACL [20].

The literature offers varying perspectives on the timeline of the ligamentisation process following graft implantation. However, multiple studies suggest that graft remodelling is a continuous biologic process, typically occurring within the first two years. Some researchers propose that this process can extend further, influenced by factors such as study design and the surgical technique employed [20].

Despite differing opinions on specific timelines, there is general agreement that graft remodelling after ligament reconstruction occurs in three distinct phases: early healing, proliferation, and maturation (or ligamentisation). One study even introduces an additional "quiescent" stage[21]. Below is an overview of these key remodelling phases and their approximate timelines following graft implantation:

Early Healing (0 to 12 months)

During the early post-operative period, significant graft necrosis is observed, particularly in the graft's centre, accompanied by low cellular activity (hypocellularity). No revascularization is detected within the graft during this time; however, host cells begin to migrate to the graft periphery. Although early signs of collagen fibril disintegration are seen in this early phase,

the overall collagen structure remains intact, leading to a gradual decline in mechanical properties. The graft is particularly vulnerable to mechanical failure, especially at the fixation site, due to inadequate biological incorporation, underscoring the need for robust mechanical support. As the healing progresses into the proliferation phase, the intra-articular portion of the graft becomes increasingly susceptible to mechanical compromise due to heightened remodelling activity, which may further weaken the graft's structural integrity [22].

Remodelling/Proliferation (2 to 18 months)

The proliferation phase is marked by intense cellular activity and changes in the extracellular matrix, contributing to the graft's lowest mechanical strength. Graft necrosis releases growth factors that promote cell migration, proliferation, and extracellular matrix synthesis, with myofibroblasts helping restore tension needed for the later ligamentisation phase. Revascularization begins during this phase and factors such as revascularization, disrupted collagen alignment, and increased collagen III synthesis reduce mechanical properties.

Maturation/Ligamentisation (10 months to 2 years and beyond)

The ligamentisation phase of ACL reconstruction involves continuous remodelling of the healing graft, aiming to mimic the morphology and mechanical strength of the intact ACL. Cellularity returns to levels comparable to the intact ACL, while vascularity stabilises, and blood supply becomes more evenly distributed throughout the graft. Collagen fibre organisation begins to resemble that of the intact ACL, although the initial loss of collagen crimp and parallel alignment from the proliferation phase is only partially restored, and the heterogeneous composition of collagen fibres is never fully recovered. Mechanical properties of the reconstructed knee improve significantly during this phase; however, studies indicate that the structural properties of the healing graft typically do not exceed 50–60% of those of the intact ACL [22].

The consensus in the literature is that the ligamentisation phase following ACL reconstruction is typically considered complete by 2 years post-implantation. However, some evidence suggests that the maturation phase may not fully conclude until around 3 years. By this time, the graft develops a ligamentous structure and enters a quiescent phase characterised by reduced cellularity and vascularity, resembling the properties of an intact ACL. During this time, the graft may continue to undergo minor adjustments in response to biomechanical stress [23].

Complications associated with graft remodelling and ligamentisation

The success of a ligament reconstruction graft is heavily dependent on the remodelling process described, as it ensures that the graft can withstand the mechanical forces applied to it when the patient returns to their normal physical activity. Disruption or delay to any of these phases (e.g., poor revascularization or insufficient fibroblast infiltration) can lead to graft failure, persistent knee instability, or other complications.

If the device did not remodel as expected, several complications would arise and an impact on the overall success of the graft and the functionality of the reconstructed ligament would

be evident in the data generated during the clinical study. When remodelling fails, the following outcomes may occur:

- Graft Weakening and Failure
- Poor Biomechanical Performance
- Chronic Pain and Inflammation
- Decreased Range of Motion & Function
- Graft Rejection or Infection

7. Suggested profile and training for users

OrthoPure® XT should only be used by orthopaedic surgeons trained in the reconstruction of knee ligaments.

8. Reference to any harmonized standards and CS applied

There are no Common Specifications currently applicable to this device.

OrthoPure® XT has been designed, developed, and manufactured in accordance with the following standards:

Standard & Issue	Standard Title
EN 556-1:2001/AC:2006	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices
EN ISO 10993-1:2020	Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process
EN ISO 10993-3:2014	Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
EN ISO 10993-5:2009	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity
EN ISO 10993-6:2016	Biological evaluation of medical devices - Part 6: Tests for local effects after implantation
EN ISO 10993-10:2023	Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization
EN ISO 10993-11:2018	Biological evaluation of medical devices – Part 11: Tests for systemic toxicity
EN ISO 10993-23:2021	Biological evaluation of medical devices – Part 23: Tests for irritation
EN ISO 11137-1:2015 +A2:2019	Sterilization of health care products – Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices

Standard & Issue	Standard Title
EN ISO 11137-2:2015 +A1:2023	Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose
ISO/TS 11137-4:2020	Sterilization of health care products. Radiation - Guidance on process control
EN ISO 11607-1:2020 +A1:2023	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems
EN ISO 11607-2:2020 +A1:2023	Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes
EN ISO 11737-1:2018+A1:2021	Sterilization of medical devices. Microbiological methods. Determination of a population of microorganisms on products
EN ISO 11737-2:2020	Sterilization of medical devices. Microbiological methods. Tests of sterility performed in the definition, validation and maintenance of a sterilization process
EN ISO 13485:2016+A11:2021	Medical devices - Quality management systems - Requirements for regulatory purposes
EN ISO 14155:2020	Clinical investigation of medical devices for human subjects – Good clinical practice
EN ISO 14630:2012	Non-active surgical implants. General requirements
EN ISO 14971:2019+A11:2021	Medical devices - Application of risk management to medical devices
EN ISO 15223-1:2021	Medical devices. Symbols to be used with medical device labels, labelling and information to be supplied. General requirements
EN ISO 20417:2021	Medical devices - Information to be supplied by the manufacturer of medical devices
EN ISO 22442-1:2020	Medical devices utilizing animal tissues and their derivatives - Part 1: Application of risk management
EN ISO 22442-2:2020	Medical devices utilizing animal tissues and their derivatives - Part 2: Controls on sourcing, collection and handling
EN ISO 22442-3:2007	Medical devices utilizing animal tissues and their derivatives - Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents
EN ISO 7010:2020+A4, A5, A6:2023	Graphical symbols — Safety colours and safety signs — Registered safety signs

9. Revision history

SSCP Revision number	Date issued	Change description	Revision validated by the Notified Body
V01	24 MAR 2025	Initial Release	☒ *Yes* *Validation Language: English* ☐ *No*

10. References

1-4. Refer to footnotes.

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TRX Orthopaedics Limited

OrthoPure® XT Ligament Reconstruction Implant

Summary of Safety & Clinical Performance

Information intended for patients

Document Revision: V01

Date issued: 24 MAR 2025

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The information presented below is intended for patients or lay persons. A more extensive summary of its safety and clinical performance prepared for healthcare professionals is found in the first part of this document.

The SSCP is not intended to give general advice on the treatment of a medical condition. Please contact your healthcare professional in case you have questions about your medical condition or about the use of the device in your situation. This SSCP is not intended to replace an Implant card or the Instructions for Use to provide information on the safe use of the device.

1. Device identification and general information

Device Trade Name	OrthoPure® XT
Manufacturer Name and Address	TRx Orthopaedics Limited Unit 3 Phoenix Court Lotherton Way Garforth Leeds LS25 2GY UK
Basic UDI	506026002XT001WA
Year of first CE Certificate	2020

TRX Orthopaedics Limited

2. Intended Use of the device

Intended Purpose	A ligament is a rope like piece of tissue that connect bones at a joint. The knee is supported by four main ligaments. The anterior cruciate ligament (ACL) is one of these knee ligaments. If the ACL and/or other knee ligaments tear, your knee will be unstable, and you will be in pain. It may also be difficult to walk. Your doctor will examine you to find out if surgery is needed to repair or replace the damaged knee ligament(s). If surgery is needed, OrthoPure® XT may be used to replace the damaged ligament(s).
Indications and intended patient groups	OrthoPure® XT may be used to replace your ACL if tissue from another part of your body cannot be used. OrthoPure® XT may be used to replace your ACL if you have had your ACL repaired before. OrthoPure® XT may be used if more than one of your knee ligaments needs replacement.
Contraindications	OrthoPure® XT should only be used in patients for which it is safe. There are some reasons why OrthoPure® XT cannot be used in some patients (contraindications). These reasons are: • It should not be used for the first repair of your ACL if you are very physically active or under 35 years old. • It should not be used if you are in severe pain or if your knee is red or swollen 24 hours before your surgery. • It should not be used if you have an infection, including an infection affecting the knee. • It should not be used if there is a risk of a new infection, for example if there is an open wound of the knee. • OrthoPure® XT is obtained from pig tissue. If you have an allergy, or object for religious reasons, the product should not be used. • It should not be used if you cannot follow the programme of care and rehabilitation following your surgery.

TRX Orthopaedics Limited

3. Device Description

Device Description	OrthoPure® XT is made from animal tissue, specifically pig tendon. OrthoPure® XT is processed and sterilised to make sure it is safe. OrthoPure® XT is available in four sizes. Each device is supplied sterile in a solution (0.9% saline). An example of a packaged device is shown below. 
Mode of Action	When OrthoPure® XT is placed into the body, it helps to support and stabilise the knee. Over time, patients' cells move into the OrthoPure® XT device and it becomes part of the body.
Accessories	There are no accessories.

TRX Orthopaedics Limited

4. Risks and warnings

General: Contact your healthcare professional if you believe that you are experiencing side effects related to the device or its use or if you are concerned about risks. This document is not intended to replace a consultation with your healthcare professional if needed.

Control of potential risks	The company that makes OrthoPure® XT is TRx Orthopaedics Ltd (Tissue Regenix). Tissue Regenix look for any problems (i.e. risks or side effects) that might happen when OrthoPure® XT is used. Tissue Regenix then take steps to reduce the chance of these problems happening as much as possible. They do this to make sure patients are safe. Tissue Regenix continually looks for risks or side effects linked to OrthoPure® XT. This information is found in a number of places including: - Complaints data for OrthoPure® XT. - Sales data for OrthoPure® XT. - Literature that reports on the use of OrthoPure® XT. - Literature about knee ligament repair surgery.
Remaining risks	The following adverse reactions have been reported in the literature or directly to Tissue Regenix: - Graft rupture/failure, residual laxity and symptoms of instability - Complications that may happen during surgery - Complications related to the surgery, for example: ▪ pain and/or numbness, knee laxity, limited knee motion, crepitus, kneeling discomfort ▪ osteoarthritis/degenerative joint disease ▪ inability to return to pre-injury levels of activity (e.g., work, sports) ▪ meniscus related injuries, neurovascular injury ▪ effusion, infection, swelling, synovitis, ▪ complications associated with fixation hardware, foreign body inflammation, complications requiring further surgical intervention (e.g. removal of fixation device) ▪ Complications relating to the surgical procedure and anaesthesia including, but not limited to, infection, release of knee stiffness, pain, and haematoma

Remaining risks *(continued)*	- Complications related to the device, for example:
	  ▪ Pain and/or numbness, knee laxity, limited knee range of motion, kneeling discomfort
	  ▪ Osteoarthritis/degenerative joint disease
	  ▪ Inability to return to pre-injury levels of activity (e.g., work, sports)
	  ▪ Effusion, infection, swelling
	- Infections, for example, superficial or deep wound infection
	- Blood clots
	- Further operation may be needed, for example due to
	  ▪ Meniscus-related injuries
	  ▪ Residual laxity and symptoms of instability
	  ▪ Complications requiring further surgical intervention (e.g., removal of fixation device)
	These are listed in the Instruction for Use (IFU) for OrthoPure® XT. The IFU for OrthoPure® XT is available at: https://www.tissueregenix.com/orthopaedics/orthopure-xt/information-for-patients/

Warnings and Precautions	The warnings and precautions for using OrthoPure® XT are listed in the IFU. There are no warnings and precautions specifically for patients.
Other aspects of safety	OrthoPure® XT is made from pig tissue. The product is processed and sterilised to ensure it is safe for use. Implant lifetime is the time from when the implant is put into your body to when the implant is either removed from your body or it is replaced by your own tissue. The time expected for the implant to be replaced by your body is 2 years. This is the time for which the device contributes to the stability of the knee joint. However, remnants of the implant could be in the body for up to 60 years. The actual lifetime of your implant may be longer or shorter than expected. It is not possible to tell if you will have issues which may require further treatment.

TRX Orthopaedics Limited

5. Summary of Clinical Evaluation and Post-Market Clinical Follow-Up (PMCF)

Clinical background	The knee is supported by a number of ligaments, including the anterior cruciate ligament (ACL). If the ACL and/or other knee ligaments tear, your knee will be unstable and you will be in pain. It may also be difficult to walk. Surgery may be needed to repair or replace the damaged ligament(s). If surgery is needed, a small instrument may be put into the knee to reach the damaged ligament(s). The doctor will repair or replace the damaged ligament(s). OrthoPure® XT may be used to replace the damaged ligament(s).
Clinical Evidence	Clinical studies allow us to see how well a product works. There is one study looking at the use of OrthoPure® XT for ACL replacement. This study looked at a number of areas to measure the success of OrthoPure® XT. Forty patients took part in this study. All had OrthoPure® XT used to replace their ACL. All patients were monitored for 2 years after surgery. This study showed that OrthoPure® XT is safe and works well for replacing the ACL. Some patients in this study agreed to continue being checked and to provide information for up to 5-years after surgery. This part of the study is now complete. This part of the study also showed that OrthoPure® XT is safe and works well for replacing the ACL. A study looking at using OrthoPure® XT to replace more than one ligament in the same knee is in progress. Patients will be monitored for 2 years after surgery. There is currently no data available from this study. A study looking at using OrthoPure® XT for ACL replacement in a wider range of people and for replacing the ACL of people who have previously had their ACL replaced but it is damaged again is also planned.

Safety	The risks of using OrthoPure® XT are mainly those related to surgery to replace knee ligaments. The benefits of using OrthoPure® XT for replacing knee ligaments are to restore stability and function of the knee. The clinical study looking at the use of OrthoPure® XT for ACL replacement showed that OrthoPure® XT can be used safely to replace damaged ligaments. Tissue Regenix continue to monitor for potential problems. They do this by collecting information from: • Patients where OrthoPure® XT has been used to replace their ligament(s); • Customer feedback and complaints. It has been determined that the benefits patients may get from the use of OrthoPure® XT outweigh the risks.

6. Possible diagnostic or therapeutic alternatives

General: When considering alternative treatments, it is recommended to contact your healthcare professional who can take into account your individual situation.

Alternative Treatments	If surgery is needed to repair or replace your knee ligament(s), there are a number of alternatives to OrthoPure® XT. These are: • Tissue from another part of your body. • Tissue from a human donor. • A man-made material. The current preferred choice of doctors is to use tissue taken from another part of your body. Your doctor will choose the treatment that best meets your medical needs.

7. Suggested training for users

Training for users	OrthoPure® XT is not to be used by patients, so no patient training is needed. The instructions provided with OrthoPure® XT will be followed by the doctor.