Executive Summary of Terminated Study:

Safety and Performance of FibroFix™ Cartilage P Implant and Drill Set for Articular Cartilage Repair within the Knee Joint

A 10-year, two-stage, multicentre, prospective, non-randomised, open-label, first-in-human clinical investigation on adult patients with a symptomatic ICRS grade 3-4 articular cartilage lesion in the anterior and central portion of the medial and/or lateral femoral condyle.

Short title: FFLEX
Investigational Devices: FibroFix™ Cartilage P and FibroFix™ Cartilage P Drill Set
Sponsor: Orthox Limited, 66 Innovation Drive, Milton Park, Abingdon, OX14 4RQ, United Kingdom
CIP reference: ORTH CIP A001, R6, 25 Apr 2022
ClinicalTrials.gov ID: NCT05560490
ISRCTN ID: 13615940
Chief Investigator: Prof Michael R. Whitehouse, Musculoskeletal Research Unit, University of Bristol
Author: Rosalyn Archer, Director of Clinical Affairs, Archer Clinical Ltd.

Statement of Compliance

The FFLEX clinical investigation has been conducted in compliance with the current ISO 14155 guidelines and applicable regulatory requirements, including the Medical Device Regulation (MDR) 2017/745.

Confidentiality Statement

EXECUTIVE SUMMARY

Short title:	FFLEX Study
Investigational Products:	FibroFix™ Cartilage P (implant) FibroFix™ Cartilage P Drill Set (site preparation instruments)
Intended Purpose:	Implant: FibroFix™ Cartilage P is designed for the resurfacing of damaged articular cartilage within the knee joint. Instruments: FibroFix™ Cartilage P Drill Set is indicated for the preparation of an implant site to resurface an articular cartilage lesion in the anterior and central regions of the femoral condyles of the knee.
Sponsor:	Orthox Limited, 66 Innovation Drive, Milton Park, Abingdon, OX14 4RQ, United Kingdom
CIP reference:	ORTH CIP A001, R6, 25 Apr 2022
ClinicalTrials.gov ID:	NCT05560490
ISRCTN ID:	13615940
Hungarian Sites:	None opened
EU sites:	None opened
UK sites:	One opened (Site 01)
UK site details:	Chief Investigator: Professor Michael Whitehouse Principal Investigator: Dr Nick Howells Musculoskeletal Research Unit, Translational Health Sciences Bristol Medical School, 1st Floor Learning & Research Building Southmead Hospital BS10 5NB Bristol United Kingdom michael.whitehouse@bristol.ac.uk
Clinical Project Manager and Author:	Rosalyn Archer, Director of Clinical Affairs, Archer Clinical Ltd. rosalyn@archerclinical.co.uk
Study Start Date:	18 August 2022
Study Early Termination Date:	14 June 2023 *(The only site activated was Site 01 (Southmead Hospital, North Bristol Trust) in the UK. Although study approvals were received from the Hungarian national Ethical Committee and Competent Authority in 2022, no site was opened in Hungary prior to termination of the study)*
Study Design:	The FFLEX study was a multicentre, prospective, non-randomised, open-label, first-in-human clinical investigation involving the evaluation of the clinical safety and performance of a new implant, FibroFix™ Cartilage P, and associated new single use and reusable instrumentation, FibroFix™ Cartilage P Drill Set, on adult patients with a symptomatic ICRS grade 3-4 articular cartilage lesion in the anterior and central portion of the medial and/or lateral femoral condyle. The FFLEX study was designed as a two-stage, non-comparative study, as follows: - **Stage I**, a cohort of six subjects to be implanted with the FibroFix™ Cartilage P, to evaluate the initial safety of FibroFix™ Cartilage P and FibroFix™ Cartilage P Drill Set across a maximum of two sites, with safety oversight being provided by an independent data management committee. - **Stage II**, an additional cohort of 69 subjects to provide a total of 75 subjects to be implanted with the FibroFix™ Cartilage P, to evaluate the long-term performance and safety of FibroFix™ Cartilage P and the FibroFix™ Cartilage P Drill Set across a larger number of sites.

	- All subjects to be followed up for 10 years post-surgery, with follow-up visits at 2 and 6 weeks, 3 and 6 months, 1 and 2 years, followed by annual safety and performance monitoring for the remaining 8 years.
Primary Objectives:	**<u>Stage I, Initial safety cohort:</u>** To demonstrate safety of FibroFix™ Cartilage P implant in a small number of subjects at 3- and 6-month post-surgery follow up, and FibroFix™ Cartilage P Drill Set intraoperatively. **<u>Stage II, Full cohort:</u>** To demonstrate performance and safety of FibroFix™ Cartilage P implant at 1-year post-surgery follow-up, and FibroFix™ Cartilage P Drill Set intraoperatively. Performance of FibroFix™ Cartilage P will be determined by change in the Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain and Function (Sport/Rec) scores from baseline at 1-year post-surgery follow-up.
Secondary Objectives:	• To demonstrate safety of FibroFix™ Cartilage P initially at 1-year and 2-years post-surgery, then will be monitored over a further 8 years follow-up. • To demonstrate performance as determined by change in KOOS subscale scores and aggregate score at 2-year post-surgery, then will be monitored over a further 8 years follow-up. • To demonstrate improvements in activity, pain and health-related quality of life at 1 year and 2 years. • To observe the implant and surrounding tissue for 2 years post-surgery to identify any changes related to the implant. To demonstrate ease of use of FibroFix™ Cartilage P and the FibroFix™ Cartilage P Drill Set.
Results:	Two subjects, 1-01 and 1-02, were recruited in the UK (Site 01), who had FibroFix™ Cartilage P implanted on 2 Dec 2022 and 27 Jan 2023, respectively. Both were followed up to their 3-month post-surgery follow-up and adhered to their rehabilitation regime throughout their post-surgical follow-up. Both did not complete the study and both were withdrawn on 5 May 2023 due to Serious Adverse Events (SAE). Baseline and follow-up clinical and questionnaire-based outcome assessments were collected from both subjects and usability questionnaires were collected from each user group after each surgery; however, statistical analysis could not be performed due to the low recruitment and short follow up duration. **Device Deficiencies:** Two Device Deficiencies (DD), both involving FibroFix™ Cartilage P Drill Set, occurred in total (one deficiency during each surgery), which did not cause any surgical problems and were not associated with any patient Adverse Events (AE) **Adverse Events:** ▪ Subject 1-01 experienced a post-surgery swelling at the index knee that did not resolve. This became a Serious Adverse Event (SAE) at 3 months post-surgery and required an Examination Under Anaesthetic (EUA), and an Aspiration procedure to be performed. The SAE did not resolve after a subsequent 2 week course of oral steroids and required reoperation to remove the implant. The patient was then withdrawn from the study. ▪ Subject 1-02 experienced synovitis, inflammation and more pain than expected at 3 months post-surgery. A Magnetic Resonance Image (MRI) was taken and raised concerns consistent with SAE

	symptom progression. The Investigator conducted a reoperation to remove the implant and the patient was withdrawn from the study. ▪ As a result of the implant removal from the first two patients recruitment was halted. After consultation involving the Data Monitoring Committee, the Sponsor made the decision to terminate the study. See Table 1 for post study closure SAE follow up details. **Endpoint analysis related to study objectives:** ▪ As only two Subjects were recruited, and both were withdrawn due to SAEs related to the FibroFix™ Cartilage P implant, the Primary Objective and all Secondary Objectives have not been met for FibroFix™ Cartilage P implant. ▪ With only two uses, data collected is considered insufficient to to demonstrate safety and performance of the FibroFix™ Cartilage P Drill Set.
Conclusions:	The FibroFix™ Cartilage P implant and the FibroFix™ Cartilage P Drill Set has failed to demonstrate safety and performance for their intended purpose.
Statement of Compliance:	The clinical investigation has been conducted in compliance with the current ISO 14155:2020 and applicable regulatory requirements, including the Medical Device Regulation (MDR) 2017/745.

Table 1: Adverse Events

Subject ID	1-01	1-01	1-02
AE #	1	2	1
Location of AE	Index knee	Index knee	Index knee
Reoperation at surgical site?	No	Yes	Yes
AE term	Ongoing swelling	Persistent swelling from knee effusion. Associated pain + delayed rehab.	Synovitis, inflammation + more than expected pain. Worrying MRI appearance consistent with this.
Additional details of event	Knee swollen since surgery - expected but not settled at 6 weeks follow-up.	10 Mar 2023: EUA, Aspiration (see Concurrent Procedure) 29 Mar 2023: 2-week course of oral steroids and gadolinium contrast MRI. 20 Apr 2023: Increased pain. Gadolinium scan shows implant related concerns. To come for removal of implant. 5 May 2023: EUA, Arthroscopy, Arthrotomy and removal of implant (see Concurrent Procedure) 24 May 2023: Histology report conclusions: left knee periarticular tissue with mixed inflammatory infiltrate suggestive of infection. Diagnosis should be confirmed by microbiology result. Microbiology negative. 25 May 2023: Knee less painful. Synovitis and swelling seem to be generally improving. 22 Jun 2023: Pain notably improved, feeling well in himself, no systemic infection symptoms, main problem reduces range of movement 5-50 degrees, persistent effusion, radiographs - stable appearance. 5th Sept 2023: Patient No.1 has been seen most recently on 3rd Aug. He is improving in terms of pain and swelling but remains restricted in terms of stiffness. He has been booked for a further MRI scan and I will review him myself once this has been performed	5 May 2023: EUA, Arthroscopy, Arthrotomy and removal of implant (see Concurrent Procedure) 24 May 2023: Histology report conclusion: right knee, periarticular tissue with a moderate inflammatory infiltrate, correlation with microbiology is recommended to exclude infection. Microbiology result no growth. 29 June 2023: Making reasonable progress; knee inflammation, swelling and pain have settled. Remain stiff and tentative; she is struggling to fully load the knee. Having regular physiotherapy and due to start hydrotherapy. Repeat MRI end of August. 5th Sept 2023: Reviewed by PI last week (31/Aug/2023) after her repeat MRI scan. She is improving symptomatically in terms of pain and swelling but remains restricted in terms of walking ability and continues to use a crutch. Her scan shows much improvement in terms of synovitis and inflammation but the knee is far from settled with residual signs of synovitis. The defect is large with a significant of bone loss from underneath the site of the previous implant. I plan to review her with a further scan in January and look to plan surgery for next year potentially if things continue to improve. 24 Jan 2024: MRI Scan – Follow up appointment

		13th Oct 2023: Examination: The swelling has subsided, and pain has improved. He does still with many activities, get focal medial joint line tenderness which is limiting his activity and more so the reduced range of movement is a problem with range of movement 0°/5°/75°. We have agreed to repeat MRI scan in Jan, Discuss in MDT following this scan and then consider surgery in the spring if all is progressing well 17 Jan 2024: MRI Scan – Follow up appointment 12th April 2024 12th Apr 2024: Review by PI. On examination: minimal tenderness, persisting focal medial tenderness, range of movement 0°/0°/100°. Soft tissue envelope around his knee is in best state it has been in for a number of years. Range of movement markedly improved since last review. Latest MRI scan (Jan 17 2024) shows further encouragement with further reduction in synovitis and further settling in the generalised evidence of inflammation that was present in scans last year. Discussed Multi-Disciplinary meeting: Medical compartment progressed beyond the state of focal treatment option. Plan: Arthrolysis and as long as sufficient movement is achieved then proceed to medial unicompartmental replacement as long as the cartilage is in a good situation laterally and patellofemoral joint. If cartilage is more damaged than expected in these compartments then we would proceed to a total knee replacement. Minutes from Meeting held on 24th April 2024 to Review the FFLEX Study SAEs following MRI and face to face review with subject:	15th March 2024 15 Mar 2024: Review with PI – details from clinic letter 10 months from removal of implant from lateral femoral condyle after failure of fixation with associated synovectomy and debridement. Significantly improved since last visit. On examination: mild residual effusion, well healed wound, excellent range of movement, good patella control. Recent MRI: Improved appearances, settled synovitis, persisting large lateral femoral condylar defect with associated inferior pole patellofemoral loss, borderline patella alta. Keen to proceed to definitive surgical treatment. Surgical options discussed including grafting, realignment, osteochondral allograft, partial or total joint replacement. For discussion at next multi-disciplinary meeting. Minutes from Meeting held on 24th April 2024 to Review the FFLEX Study SAEs following MRI and face to face review with subject: The joint on the index surgery side is looking good. The defect will be treated in isolation with surgery to undergo debridement and application of bone graft to restore the bone stock (new bone to fill the hole left by the implant removal from the original lesion). If any issues remain, the patient may have focal resurfacing (*e.g*. hemicap implant) in the future. The SAE related symptoms for both patients in the FFLEX Study are now greatly reduced or resolved; regards movement, pain and function, all of which are improved. Neither has a 'normal' knee and each will need a surgical intervention. It has been decided to close the SAEs as 'Resolved with sequelae' and conduct the final Close Out Visit for the Study.

			Patient doing much better. The symptoms in the index knee have calmed down. Slightly less good than knee before the study intervention – At the start of the SAE he had bad stiffness allowing for 20-60degrees movement; this is now improved to 5-95 degrees. There is some reciprocal damage to the tibial side of the treated side of the joint (medial). The patient will undergo a partial (unicondular) joint replacement of the medial side of the index knee and cartilage debridement/resection any synovitis of the index knee in the week beginning 29th April 2024. If this does not resolve his knee problems, he will have a total knee replacement in the future. The SAE related symptoms for both patients in the FFLEX Study are now greatly reduced or resolved; regards movement, pain and function, all of which are improved. Neither has a 'normal' knee and each will need a surgical intervention. It has been decided to close the SAEs as 'Resolved with sequelae' and conduct the final Close Out Visit for the Study.	
	Start date	03 Dec 2022	03 Mar 2023	19 Apr 2023
	Date of site awareness	19 Jan 2023	09 Mar 2023	19 Apr 2023
Causality to the Investigational Device or Procedure:	**Relationship to Investigational Device**	Probably related	Possibly related	Causal relationship
	Relationship to Procedure	Probably related	Possibly related	Causal relationship
	Rationale for causality assessment	Swelling expected following surgery. Ongoing swelling probably related to device or procedure.	Symptoms may or may not be related. Further investigations are planned urgently.	Pain implant site. MRI shows implant related concerns.
	Severity	Moderate	Moderate	Severe

Serious AE?	**Yes / No**	No	Yes	Yes
	Date event first became serious	N/A	09 Mar 2023	20 Apr 2023
	Criterion for seriousness	N/A	**2.** Led to a serious deterioration in the health of the subject that resulted in any of the following: **iii.** In-patient or prolonged hospitalization	**2.** Led to a serious deterioration in the health of the subject that resulted in any of the following: **iii.** In-patient or prolonged hospitalization **iv.** medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function
Action taken		None	Medication Gadolinium contrast MRI Concurrent procedure Study withdrawal	Concurrent procedure Study withdrawal
Outcome of Event		Ongoing	Ongoing	Ongoing
End date with sequalae		Upgraded to SAE on 09 Mar 2023*	Followed up post patient withdrawal until 24th April 2024	Followed up post patient withdrawal until 24th April 2024