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HEALTH TECHNOLOGY BRIEFING
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PLX-PAD for injured gluteal musculature following arthroplasty

NIHRIO ID	9619	**NICE ID**	10416
Developer/Company	Pluristem Therapeutics Inc	**UKPS ID**	N/A

Licensing and market availability plans	Currently in Phase III clinical trials.

SUMMARY

PLX-PAD is in development for the treatment of hip fractures. Hip fractures are when the bones related to the hip are damaged. They can occur at any age, however it is most common in the older population. This leads to pain and difficulty moving. Hip replacements, surgery which replaces damaged areas of the hip with artificial implants, is a common treatment for hip fractures. As the surgery requires cutting the muscles either at the front or back of the pelvis, to access the hip and leg bone, this can lead to muscle weakening. There are no medicinal options for treating muscle injury after hip replacement.

PLX-PAD is an intramuscular (into muscle) injection that includes cells to promote muscle regeneration. PLX-PAD cells respond to the body's distress signals, which are sent from the site of injury, by secreting proteins to help the body to i) grow blood vessels to supply damaged tissue, ii) heal muscle and iii) dampen the inflammatory response (which is aggravated by injury). PLX-PAD is in development to promote muscle injury recovery for people undergoing hip replacement, which may reduce recovery time in this patient population.

PROPOSED INDICATION

Adult patients aged 60 to 90 years with muscle injury following arthroplasty for hip fracture.[1]

TECHNOLOGY

DESCRIPTION

PLX-PAD (PLacental-eXpanded mesenchymal-like adherent cells, emiplacel, allogenic ex-vivo expanded placental ADherent stromal cells) are cells isolated from full-term placentae and express immunomodulatory, anti-apoptotic, pro-angiogenic, and anti-fibrotic proteins, which are key to muscle regeneration. PLX-PAD cells respond to chemical distress signals from tissues that have been damaged by ischaemia (inadequate blood flow), muscle trauma, or inflammation, by secreting a range of therapeutic proteins that trigger the body's own repair mechanisms. These secreted proteins drive the body to grow collateral blood vessels to bring oxygenated blood to ischaemic tissue, heal damaged muscle, and dampen inflammation. PLX-PAD cells also modulate the immune system, which plays a central role in the body's response to injuries.[2,3]

In the phase III clinical trial (NCT03451916), during the surgical procedure (total hip arthroplasty or hemiarthroplasty), patients will receive 150×106 PLX-PAD cells (10×106 cells/mL) in a mixture containing 10% dimethyl sulfoxide (v/v), 5% human serum albumin (w/v) and PlasmaLyte by intramuscular injection.[1]

INNOVATION AND/OR ADVANTAGES

No regenerative approach has thus far been shown to be effective in skeletal muscle injuries. There are currently no therapeutic options for regenerating injured skeletal muscles.[2]

NICE have no recommendations for treating muscle injury following arthroplasty for hip fracture.[4]

In the phase I/II (NCT01525667) clinical trial PLX-PAD showed signs of accelerating healing through histology and gluteus medius strength in comparison with a placebo, which could improve recovery time for patients. In addition, there were no PLX-PAD associated adverse events up to 2 years after treatment.[2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

PLX-PAD does not currently have Marketing Authorisation in the EU/UK for any indication.

PLX-PAD may meet the criteria for an advanced therapy medicinal product (ATMP) classification by the European Medicines Agency (EMA).[5]

PLX-PAD is in phase II and III clinical trials for:[6]

- COVID-19
- Critical limb ischaemia with minor tissue loss

PATIENT GROUP

DISEASE BACKGROUND

The hip is a ball and socket joint that connects the leg to the pelvis by the top of the thigh bone (femoral head – the "ball"), cartilage and acetabulum ("socket"). This allows diverse movement of the leg due to the ability to flex and rotate. Hip bones experience wear and tear due to ageing, and this can also be contributed by fracture, arthritis, or bone death due to lack of blood supply. Cartilage supports the femoral bone and pelvis, which acts as a cushion between the two, and damage to this results in irregularities and grinding of the bones, which can cause pain and loss of movement.[7,8]

Hip replacements are offered to persons that have issues with pain and restricted movement because of worn or damaged hip joints.[8,9] Most common reasons for hip replacement include osteoarthritis, rheumatoid arthritis, septic arthritis, hip fracture, and bone dysplasias (disorders that result in unusual bone growth). Hip fractures are breaks at the top of the femur, which are caused by trauma through falls or injury. Osteoporosis, bone weakening, can increase the risk of developing hip fractures.[10] Any adult can be considered for a hip replacement, however it is most commonly undertaken in people between 60-80 years old.[9]

Hip replacement options include:

- Total hip replacement (total hip arthroplasty)
- Partial hip replacement (hemiarthroplasty)
- Hip resurfacing

Total hip arthroplasty (THA) involves the replacement of the ball and socket joint, and the femoral head and neck (top of the thigh bone), with artificial implants. Hemiarthroplasty (HA) is replacement of one side of the hip joint, as opposed to its entirety.[11] Hip resurfacing preserves natural bone including the femoral head by placing a metal covering over it and implanting a metal cup-shaped lining into the acetabulum. This is typically offered to persons with hip issues who are physically active and under 60 years old.[7]

THA can be done posteriorly, through dissection of gluteus maximus, or anteriorly, through tensor fascia lata (TFL). These surgeries are named after the locations of the muscles required to be dissected in order to access the hip.[8] There are other surgical approaches to hip replacement, however posterior and anterolateral approaches are the most common.[12] After THA muscle strength can be weakened as a result of muscle dissection and subsequent healing process.[13-16]

Around 1 in 3 adults over 65 years old will have at least one fall a year and half will have falls more frequently. This can cause damage to bones, including the hip bone.[17] In 2018/19 most hip replacement patients were aged 50 years or older (93.8%), with patients aged 50-69 accounting for 41.9% compared to 51.9% for patients over 70 years old.[18]

CLINICAL NEED AND BURDEN OF DISEASE

In England, 2019-20, there were 75,929 finished consultant episodes (FCE) of patients with a diagnosis of fracture of neck of femur (ICD-10 code S72.0) resulting in 813,678 FCE bed days and 38 day cases.[19]

In England, 2019-20, there were 28,128 FCE for procedures involving prosthetic replacement of head of femur (OPCS4 codes W46-48) resulting in 350,336 FCE bed days and 7 day cases. There were also 27,967 FCE for procedures involving hybrid prosthetic replacement of hip joint (OPCS4 codes W93-95) resulting in 112,044 FCE bed days and 89 day cases.[19]

No specific statistics are available regarding incidence and nature of muscle damage during these procedures.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Post-THA treatment is focused on restoring mobility through a rehabilitation programme, utilising exercise regimes and physiotherapy. Rehabilitation is coordinated by a multi-disciplinary team, which can include physiotherapists, occupational therapists, social workers, orthopaedic surgeon, geriatrician and liaison nurse.[20]

CURRENT TREATMENT OPTIONS

There are no current medicinal treatment options for the treatment of muscle injury after THA.[2,4]

PLACE OF TECHNOLOGY

If licenced, PLX-PAD will provide the first specific medicinal treatment for patients with muscle injury following THA.

CLINICAL TRIAL INFORMATION

Trial	**NCT03451916; 2017-005165-49; Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, Designed to Determine the Efficacy, Safety, and Tolerability of Intramuscular Administration of Allogeneic PLX-PAD Cells for the Treatment of Muscle Injury Following Arthroplasty for Hip Fracture**

	Phase III – Recruiting **Location(s):** EU (including UK) and United States **Primary completion date:** June 2021
Trial design	Randomised, double-masked, parallel assignment.
Population	N=240 (planned); male or female; aged 60 to 90 years old; suffering low energy trauma with intracapsular neck of femur fracture; planned to be treated with THA or hemi-arthroplasty (HA) within 48 hours of hospital admission and 72 hours post fracture.
Intervention(s)	IM injection of 150×106 PLX-PAD cells (10×106 cells/mL) in a mixture containing 10% dimethyl sulfoxide (v/v), 5% human serum albumin (w/v) and PlasmaLyte.
Comparator(s)	Matched placebo.
Outcome(s)	Short Physical Performance Battery (SPPB) score [Time Frame: Week 26.] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**NCT01525667; A Phase I/II, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Intramuscular Injections of Allogeneic PLX-PAD Cells for the Regeneration of Injured Gluteal Musculature After Total Hip Arthroplasty** **Phase I/II – Completed** **Location(s):** Germany **Study completion date:** June 2015
Trial design	Randomised, double-masked treatment.
Population	N=20 (actual); male or female; participants aged 50 to 75 years old with a scheduled Total Hip Arthroplasty (THA)
Intervention(s)	Single course with multiple IM injections of 150M PLX-PAD or 300M PLX-PAD.
Comparator(s)	Matched placebo.
Outcome(s)	Change From Day 0 to Week 26 in the Maximal Voluntary Isometric Contraction (MVIC) Moment (in Nm) of the Injured Side to Assess Gluteus Medius Strength. [Time Frame: Day 0 to Week 26] Change from Visit 2 (Day 0) to Week 26 in the MVIC (Nm) of the injured side as measured by isometric dynamometry to assess Gluteus Medius force strength. See trial record for full list of other outcomes.
Results (efficacy)	Improved gluteus medius strength was noted as early as Week 6 in the treatment groups. Until Week 26, the low-dose (150M) group outperformed the high-dose (300M) group and reached significantly improved strength compared with

	placebo [150 M vs. placebo: P = 0.007 (baseline adjusted; 95% confidence interval: 7.6, 43.9); preoperative baseline values mean ± SE: placebo: 24.4 ± 6.7 Nm, 150 M: 27.3 ± 5.6 Nm], mirrored by an increase in muscle volume [150 M vs. placebo: P = 0.004 (baseline adjusted; 95% confidence interval 6.0, 30.0); preoperative baseline values GM volume: placebo: 211.9 ± 15.3 cm3, 150 M: 237.4 ± 27.2 cm3]. Histology indicated accelerated healing after cell therapy. Biomarker studies revealed that low-dose treatment reduced the surgery-related immunological stress reaction more than high-dose treatment (exemplarily: CD16+ NK cells: Day 1 P = 0.06 vs. placebo, P = 0.07 vs. 150 M; CD4+ T-cells: Day 1 P = 0.04 vs. placebo, P = 0.08 vs. 150 M).[2]
Results (safety)	Not observed relevant PLX-PAD-related adverse events at the 2-year follow-up.[2]

ESTIMATED COST

The cost of PLX-PAD is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Joint replacement (primary): hip, knee and shoulder (NG157). June 2020
- NICE clinical guideline. Hip fracture: management (CG124). May 2017
- NICE quality standard. Hip fracture in adults (QS16). May 2017

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Orthopaedics (Adult). D10/S/a

OTHER GUIDANCE

- British Orthopaedic Society & British Hip Society. Best Practice for Hip Arthroplasty: Surgery Documentation. 2019[21]
- Holzwarth U, Cotogno G. Total hip arthroplasty: State of the art, prospects and challenges. European Commission Joint Research Centre. 2012[22]

ADDITIONAL INFORMATION

Pluristem Therapeutics Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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