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HIPGEN: a randomized, multicentre phase III study using intramuscular PLacenta-eXpanded stromal cells therapy for recovery following hip fracture arthroplasty

A STUDY DESIGN

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Aims

The aim of the HIPGEN consortium is to develop the first cell therapy product for hip fracture patients using PLacental-eXpanded (PLX-PAD) stromal cells.

Methods

HIPGEN is a multicentre, multinational, randomized, double-blind, placebo-controlled trial. A total of 240 patients aged 60 to 90 years with low-energy femoral neck fractures (FNF) will be allocated to two arms and receive an intramuscular injection of either 150 × 10^6 PLX-PAD cells or placebo into the medial gluteal muscle after direct lateral implantation of total or hemi hip arthroplasty. Patients will be followed for two years. The primary endpoint is the Short Physical Performance Battery (SPPB) at week 26. Secondary and exploratory endpoints include morphological parameters (lean body mass), functional parameters (abduction and handgrip strength, symmetry in gait, weightbearing), all-cause mortality rate and patient-reported outcome measures (Lower Limb Measure, EuroQol five-dimension questionnaire). Immunological biomarker and in vitro studies will be performed to analyze the PLX-PAD mechanism of action. A sample size of 240 subjects was calculated providing 88% power for the detection of a 1 SPPB point treatment effect for a two-sided test with an α level of 5%.

Conclusion

The HIPGEN study assesses the efficacy, safety, and tolerability of intramuscular PLX-PAD administration for the treatment of muscle injury following arthroplasty for hip fracture. It is the first phase III study to investigate the effect of an allogeneic cell therapy on improved mobilization after hip fracture, an aspect which is in sore need of addressing for the improvement in standard of care treatment for patients with FNF.

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Introduction

Medical care of the elderly is central to European efforts to ensure healthy ageing.[1] Femoral neck fracture (FNF) within the older adult population represents a relevant socio-economic concern.[2,3] It is associated with a substantially increased risk of death and major morbidity in older adults, with 33% cumulative one-year mortality rates.[4] Post-traumatic and postoperative mobility impairment results in associated adverse events, such as thromboembolism and pneumonia.[5] Operative treatment of hip fractures is the only viable option in almost all cases in order

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to facilitate early mobilization, and to reduce the risk of complications associated with immobilization.[6]

Patients treated with arthroplasty have the ability of full weightbearing immediately after surgery, but nevertheless exhibit poor mobility, low quality of life, and high institutionalization rates.[7,8] For the frail and often sarcopenic FNF patients, surgery results in a significant stress reaction as well as iatrogenic injury to the periarticular musculature of the hip.[9,10]

Consequently, a high unmet clinical need exists to improve recovery following FNF surgery to enable the older adult patient cohort to regain physical function and return to activities of daily life. We therefore propose a randomized controlled trial of an intervention designed to enhance muscle performance and hence improve mobilization.

PLacental-eXpanded stromal cells (PLX-PAD) are a cell-based medicinal product, composed of ex-vivo-expanded adherent human placenta-derived stromal cells in a sterile cellular dispersion for injection (DOSES: allogenic, placental, adherence isolated and expanded, high expression of CD105, CD73 and CD29, and absence of expression of CD45, CD34, CD14, CD19, and human leucocyte antigen - DR isotype (HLA-DR) surface molecules, intramuscular injection. DOSES: donor, origin tissue, separation method, exhibited cell characteristics, and site of delivery as published by Murray et al[11] in the international expert consensus on a cell therapy communication tool). PLX-PAD cells are mesenchymal stromal cell (MSC)-like cells, exhibiting similar qualities to MSCs and sharing similar surface characteristics,[12,13] but they do not differentiate into downstream cell types of the mesodermal lineage in vitro.

The International Society for Cellular Therapy defines the following minimal criteria for MSCs to fulfill: plastic-adherent (standard culture conditions); must express CD105, CD73 and CD90; lack expression of CD45, CD34, CD14 or CD11b, CD79alpha, or CD19 and HLA-DR surface molecules; and differentiate into osteoblasts, chondroblasts or adipocytes in vitro.[14]

PLX-PAD cells are characterized by a high expression of CD105, CD73 and CD29, and absence of expression of CD14, CD19, CD45, CD34, and HLA-DR surface molecules.[15] Furthermore, they do not express CD31 (endothelial cell marker) or other haematopoietic or trophoblastic factors on their membrane.[16]

A comprehensive marker profile of PLX-PAD cells in comparison to both bone marrow and amniotic membrane MSCs has already been published.[17,18]

While PLX-PAD cells exhibit a membrane marker expression typical of classical MSCs, they have a minimal ability to differentiate in vitro into cells of mesodermal lineage.

The main advantages of PLX-PAD cells are the possibility to use them as an "off-the-shelf" product, their thorough characterization (not possible for autologous cell products), and their strong immunomodulatory and regenerative qualities.[19] PLX-PAD can be administered without HLA matching due to their low immunogenicity.[20] The therapeutic potential of PLX-PAD has been evaluated in both in vitro and in vivo studies, which have supported their proposed mechanism of action of inducing muscle regeneration, positively influencing angiogenesis, and exhibiting immunomodulatory effects.[19] These properties support the use of PLX-PAD as a therapy addressing the complex disease burden of hip fracture patients, which includes the postoperative stress reaction, impaired mobilization due to iatrogenic periarticular muscle injury, and the serious physiological imbalance triggered by injury and consequent surgery.[17] Muscle regeneration is supported by the secretion of soluble factors such as Galectin-1, Osteopontin, Follistatin, and insulin-like growth factor binding protein-3.[17] Immunomodulatory properties of PLX-PAD include the ability to increase secretion of the immuno-regulatory cytokines interleukin (IL)-10 and IL-1Ra.[13]

Paving the way for the HIPGEN study. Recent research indicates that the para- and endocrine functions of MSCs play the decisive role in the enhanced regeneration of injured tissues. The effects of MSC treatment on muscle injuries have been investigated by our group in various preclinical experimental set-ups,[21–25] demonstrating their positive effect on muscle regeneration. Additionally, we have performed a pilot phase I/IIa clinical trial designed to evaluate the safety and efficacy of PLX-PAD cells in 20 patients undergoing hip arthroplasty due to degenerative arthritis of the hip.[17] Patients received either placebo or PLX-PAD cells via intramuscular injection. An important finding was a significant increase in the contraction force of the abductor muscles and in muscle volume in the group treated with PLX-PAD cells compared to placebo after a six-month follow-up. In the contralateral gluteus medius (GM) muscle, an increased contraction force without increased volume was observed. The early postoperative immunological stress reaction was significantly reduced. No safety concerns were noted during the trial and follow-up period.[17] The study results revealed that older adults with FNF represent the best cohort for this phase III trial.

Aims and objectives. The HIPGEN study is designed to determine the efficacy, safety, and tolerability of intramuscular injections of allogenic PLX-PAD cells for improving recovery following hip arthroplasty (either total hip arthroplasty (THA) or hemiarthroplasty (HA)) for FNFs in older adult patients.

Methods

The Consolidated Standards of Reporting Trials (CONSORT) statement[26] has been followed when designing the study.

Table I. Primary efficacy endpoint as well as secondary efficacy endpoints, exploratory endpoints, safety endpoints, and tolerability endpoints of the HIPGEN study.

Primary efficacy endpoint
SPPB score at week 26.
Secondary efficacy endpoints
1. Hip abduction strength of the injured leg at week 26.
2. Change from baseline to Week 52 in LEM (retrospective collection of pre-fracture LEM at day 5).
3. SPPB score at week 52.
4. All-cause mortality rate.
Exploratory endpoints
1. Change from baseline to week 26 in LEM.
2. Hip abduction strength of the uninjured leg at weeks 26 and 52.
3. Hip abduction strength of the injured leg at week 52.
4. Change from week 6 to weeks 26 and 52 in total appendicular lean body mass DEXA).
5. Change from week 6 to weeks 26 and 52 in lean body mass of the injured leg (DEXA).
6. Lean Body Mass of the injured leg at week 26 (DEXA).
7. Change from baseline to weeks 26, 52, and 104 in EQ-5D-5L (retrospective collection of pre-fracture EQ-5D-5L at day 5).
8. PGI-S
9. Change from baseline to week 52 in hand grip strength.
10. Six Minute Walk Test at week 26 and 52.
11. Number of physiotherapy sessions done with a professional during the first six weeks post-surgery.
12. Proportion of subjects with complete weightbearing as measured with instrumented insoles at week 6.
13. Symmetry in gait as measured with instrumented insoles at weeks 26 and 52.
14. Annualized rate of hospital readmissions.
15. SPPB sub-score at week 26: four metres gait speed (time to walk four metres).
16. SPPB sub-score at week 26: five chair stands test (time to rise from a chair and return to the seated position five times without using arms).
17. SPPB sub-score at week 26: balance test (ability to stand with the feet together in the side-by-side, semi-tandem, and tandem positions).
18. Symmetry in gait (3D motion analysis) at week 26 (in selected study sites).
19. Pelvic shift (3D motion analysis) at week 26 (in selected study sites).
Safety endpoints
1. Adverse events and serious adverse events.
2. Safety laboratory data (haematology, biochemistry).
3. Vital signs.
4. Physical examination findings.
Tolerability endpoints
1. Proportion of subjects (%) who prematurely discontinue from the study.
2. Proportion of subjects (%) who prematurely discontinue from the study due to adverse events.

DEXA, dual-energy x-ray absorptiometry; EQ-5D-5L, EuroQol five-dimension five-level questionnaire; LEM, Lower Extremities Measure; PGI-S, patient global impression of severity; SPPB, Short Physical Performance Battery.

Primary objective. The primary objective of this study is to confirm the efficacy of PLX-PAD in the mobilization recovery of subjects following surgery for FNF. The Short Physical Performance Battery[27] (SPPB) at week 26 after PLX-PAD or placebo injection serves as the primary endpoint for evaluating efficacy.

Secondary efficacy endpoints as well as exploratory endpoints, safety endpoints and tolerability endpoints are listed in Table I.

Study design. The trial was designed as a phase III, multicentre, multinational, randomized, double-blind, placebo-controlled study. The allocation ratio was chosen 1:1.

A total of 21 study centres in six countries are included in the study. The main study period extends from initial screening to 52 weeks post-treatment follow-up, with patient visits at days 1 and 5 and weeks 6, 12, 26, and 52, and long-term follow-up at week 104 (patient visit). Data will be analyzed for the primary objective after last patient out at week 26. Some clinical research organization (CRO) and sponsor personnel will be unblinded; however, site and study personnel will remain blinded until the completion of the week 104 follow-up visit.

Study design and study specific periods are schematically illustrated in Figure 1.

Eligibility. Eligible study participants are patients of both sexes suffering from a medial FNF after low-energy trauma (due to osteopenia/osteoporosis as underlying disease), between the ages 60 and 90 years, who are able to walk at least three meters with or without walking aids before fracture and with an American Society of Anesthesiologists (ASA)[28] score ≤ 3. Only patients scheduled for implantation of a THA or HA via a direct lateral approach are included. Table II shows the main inclusion and exclusion criteria of the trial.

Consent. Diagnosed hip fractures require urgent operative intervention. The primary treatment and medical first contact must focus on preparing for surgery and definitive treatment. The occurrence of any kind of injury is mentally distressing for a patient, and as described in other clinical trials addressing hip fractures, the initial phase of anxiety, pain, and agitation can hamper the explanation of the study content.[29]

In the present study, extra care is taken not to burden vulnerable patients with decision pressure. If present, the next of kin are included in conversations and explanations about the study, and patients are able to consult their next of kin for advice in the informed consent process. Written consent is obtained from each subject to be involved in the clinical study by using the ethics committee approved informed consent form prior to the conduct of any study-related activity. The subjects are also instructed that their participation is voluntary and they are free to withdraw their consent and discontinue their participation at any time without prejudice.

Randomization and blinding. If eligible and after giving informed consent, subjects are randomized using a 1:1 allocation scheme to treatment with either 150 million PLX-PAD cells or placebo.

To attempt to eliminate known and unknown confounding factors within the study, a dynamic randomization procedure using an interactive response technology is used, balancing the treatment groups

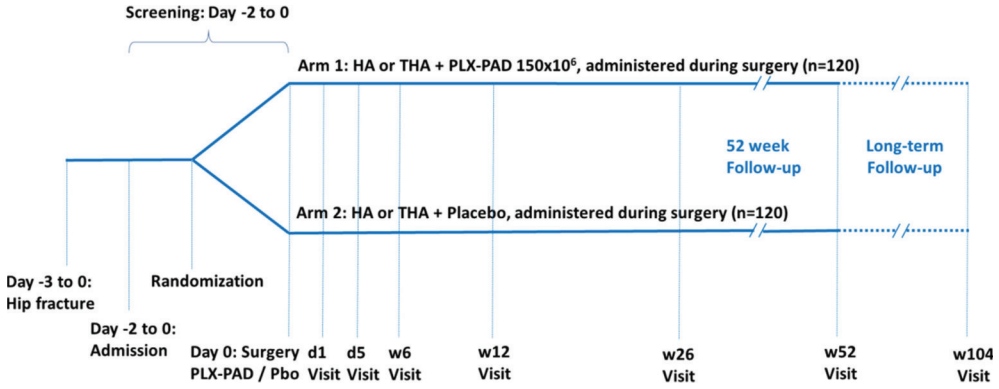

Fig. 1

Schematic study design of the HIPGEN trial. Main study period comprises four periods (screening and pre-surgery; surgery and treatment with placenta-derived adherent stromal cells (PLX-PAD) or placebo (Pbo); hospital follow-up until discharge; follow-up period of 104 weeks). d, day; HA, hemiarthroplasty; placebo; THA, total hip arthroplasty; w, week.

according to geographical region, THA versus HA, age groups (< 75 and ≥ 75 years), and sex.

The HIPGEN study is designed as a double-blind study. The study subjects, investigators, blinded study associates, and study site personnel directly in contact with the study subjects are fully blinded throughout the study. Only the study associates responsible for preparation of the investigational product or placebo are unblinded; they are not in contact with the study subjects and do not take part in further study processes. The injections are prepared by unblinded site staff so that blinded team members remain unaware of the treatment assignment. In case of medical need, unblinding of each case can be guaranteed throughout the study.

Post-randomization withdrawals. The main causes of participant withdrawal from the study are intolerable or serious adverse events, other safety concerns for participants' health, general safety concerns, participant non-compliance, or incapacitation within the study period. Participants can retract their informed consent at any time within the study process.

Study procedure and administration of investigational product. Subjects are scheduled to undergo THA or HA via a direct lateral approach within 48 hours of admission and up to 72 hours following fracture. During the surgical procedure, PLX-PAD treatment or placebo is administered via ten intramuscular injections of 1.5 ml each (15 ml cumulative volume) delivered to the injured GM muscle of the affected leg after suturing the muscle (Figure 2). The PLX-PAD treatment consists of 150 million PLX-PAD cells total (10 million cells/ml) in PlasmaLyte with 10% DMSO (v/v) and 5% HSA (w/v). The placebo contains only the carrier solution (10% DMSO (v/v) and 5% HSA (w/v) in PlasmaLyte).

Data management. The clinical data are collected at all study centres within the clinical part of the study. Further data from tissue and blood samples are collected in the specialized laboratory and research centres, included within the study consortium (Charité-Universitaetsmedizin Berlin, Germany, University of Oxford, Oxford, UK, Centro di Ricerca E. Menni, Fondazione Poliambulanza-Istituto Ospedaliero, Brescia, Italy).

All collected data are entered by the on-site study staff into Medidata Rave, an electronic data capture system that is Food and Drug Administration (FDA) 21 CFR Part 11 and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice compliant, and automatically keeps an audit trail of all entries and corrections to the electronic case report forms. Data are monitored on site as well as centrally to ensure its accuracy and integrity.

Endpoints. The primary study endpoint is the SPPB at 26 weeks post-intervention. The SPPB is a widely accepted instrument measuring the physical performance and state of physical disability in older adults, and has been shown to be a good predictor of mortality, nursing home admission, and hospitalization.[30–32] The SPPB consists of three parts analyzing the patient's physical state: standing balance, walking, and chair rise. Standing balance is assessed through the patient's ability to stand in three positions for ten seconds each: 1) feet in parallel and as close as possible, 2) semi-tandem stance, and 3) tandem stance. Walking is measured through gait speed over four metres (with or without walking aids, as used pre-surgery). The walking assessment is repeated twice, and only the shorter time is used for further analysis. In the chair rising test, participants are asked to rise from and then sit down on a chair five times as fast as possible, while their arms remain crossed. Each of the three parts is scored from 0 (not able) to 4 (able), resulting in a scale with a maximum total score of 12 points, with a higher score indicating higher mobility (0 points showing worst mobility).[27]

Secondary endpoints (Table I) include the Lower Extremities Measure (LEM)[33] and assessment of abduction strength. The LEM is a short and simple patient-reported

Table II. Inclusion and exclusion criteria. There are slight differences in inclusion/exclusion criteria between main protocol version (used in USA, Israel, and Bulgaria) and the country-specific versions of Germany, UK, and Denmark.

Inclusion criteria*
1. Male or female subjects.
2. Subjects 60 to 90 years of age, inclusive, at the time of screening.
3. Subjects suffering low-energy trauma with intracapsular femoral neck fracture.
4. Planned to be treated with THA or HA, via direct lateral approach, within 48 hours of hospital admission and 72 hours post-fracture.
5. ASA score ≤ 3.
6. Subjects able to walk ten feet/three metres before the fracture (with or without walking aids and without help of a person most of the time), based on self-report.
7. Subject has signed an informed consent form.
Exclusion criteria†
1. Any significant musculoskeletal (including ectopic bone formation), neurological, or neuromuscular disease causing muscle weakness and/or affecting mobility at the time of screening, based on the investigator's judgment.
2. Current fracture is due to bone pathology other than osteoporosis (as diagnosed on the preoperative radiograph) or due to high-energy trauma (e.g. car accident).
3. Planned orthopaedic surgery on lower limbs (excluding hip arthroplasty) within the next 12 months.
4. Diabetes mellitus with glycosylated haemoglobin (HbA1c) > 10% at screening.
5. Known current or history of proliferative retinopathy or diabetic retinopathy.
6. Known active Hepatitis B virus or Hepatitis C virus infection at screening.
7. Known HIV infection, severe uncontrolled inflammatory disease, or severe uncontrolled autoimmune disease (e.g. ulcerative colitis, Crohn's disease).
8. Immunosuppression due to illness or medication (e.g. high dose corticosteroids, calcineurin inhibitors, anti-TNF, anti-IL-6, anti-p40; prednisone equivalent lower than 10 mg/day is accepted) at the time of screening.
9. AST or ALT > 3 × ULN.
10. Subjects on renal arthroplasty therapy or with eGFR < 15 ml/min/1.73 m^2 (based on MDRD equation).
11. Severe congestive heart failure symptoms (NYHA Stage IV) at screening.
12. Known uncontrolled severe hypertension.
13. Treatment with anabolic steroids within six months prior to screening.
14. Albumin < 2.5 g/dl.
15. Active malignancy or history of malignancy within three years prior to screening with the exception of successfully resected basal cell carcinoma or skin squamous cell carcinoma not located on the injured leg.
16. Known diagnosis of moderate to severe dementia based on subject's medical history, past Mini-Mental State Examination test score of ≤ 18 or equivalent, or severe psychiatric disorder.
17. Known allergies to any of the following: DMSO, HSA, bovine serum albumin, PlasmaLyte, and gentamicin (and other aminoglycoside antibiotics).
18. History of allergic/hypersensitivity reaction to any substance having required hospitalization and/or treatment with IV steroids/epinephrine, history of acute transfusion reaction, known allergy to more than three allergens, or in the opinion of the investigator the subject is at high risk of developing severe allergic/hypersensitivity reactions.
19. Known history of severe atopic disease (including but not limited to chronic urticaria, respiratory allergy requiring oral steroids), known history of uncontrolled asthma (Global Initiative for Asthma III-IV).
20. Pulmonary disease requiring supplemental oxygen treatment on a daily basis.
21. Known history of drug or alcohol abuse in the past 12 months, based on self-report or medical record.
22. History of autologous/allogenic bone marrow or solid organ transplantation.
23. Exposure to allogenic cell-based therapy in the past or exposure to autologous cell therapy in the last 12 months before screening.
24. Current evidence/sign supporting an assessment of life expectancy of less than six months, for reasons other than hip fracture (HF) complications, based on the investigator's judgment.
25. Subject is currently enrolled in an investigational device or drug trial, or has not yet completed a period of at least 30 days since ending other investigational device or drug trial(s).
26. Subject is detained or institutionalized under a court order or administrative order.
27. In the opinion of the investigator, the subject is unsuitable for participating in the study.

*Subjects must meet all of the inclusion criteria listed below to be eligible for the study.
†Subjects with any one of the exclusion criteria listed below will not be eligible for the study.
ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; DMSO, dimethyl sulfoxide; eGFR, estimated glomerular filtration rate; HA, hemiarthroplasty; HF, hip fracture; HSA, human serum albumin; IL-6, interleukin-6; IV, intravenous; MDRD, Modification of Diet in Renal Disease; NYHA, New York Heart Association; THA, total hip arthroplasty; TNF, tumour necrosis factor; ULN, upper limit of normal.

outcome measure (PROM) that has been shown to be a reliable, valid, and responsive tool to evaluate function in patients with a hip fracture. Abduction strength is measured with a handheld dynamometer to assess gluteal muscle function. Patient assessment via SPPB, LEM, and strength measurement makes it possible to perform follow-up of patients at their homes, which has proven useful, particularly during the COVID-19 pandemic.

Exploratory endpoints (Table I) include morphological analyses performed by dual-energy x-ray absorptiometry (DEXA), handgrip strength assessment, and individualized gait analysis. Instrumented insoles (Novel; Germany) are used at all sites for individualized gait analyses specifically assessing symmetry in gait and weightbearing. Additionally, at the University of Oxford and at Charité-Universitätsmedizin Berlin, full 3D gait analysis is performed.

Routine safety labs including blood chemistry panel and complete blood count are obtained at the visits and assessed in a central lab. The values are available to the site staff. Additionally, at select study sites, blood samples are obtained at various timepoints to assess circulating

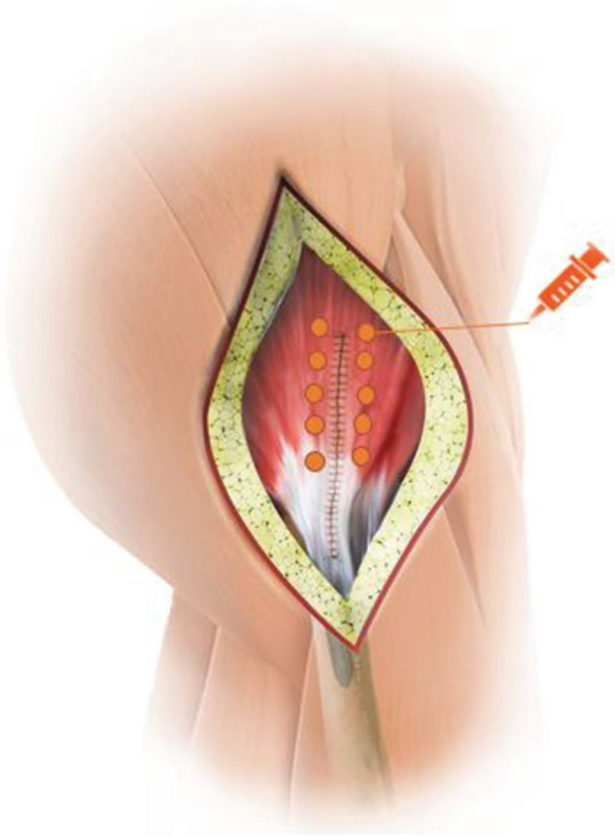

Fig. 2
The ten sites of injection after suture using the direct lateral approach.

immune cell subset composition, systemic inflammation (plasma cytokine level), immune cell cytokine secretion profile, and other markers to assess the body's response to PLX-PAD.

Sample size calculation. This study is powered to demonstrate the superiority of PLX-PAD as compared to placebo treatment in the primary as well as secondary endpoints. For the SPPB (its value at week 26 serves as the primary endpoint), we assume: a) two-sided test with α level of 5%; b) SPPB is measured at weeks 6, 12, 26, and 52 (the standard deviation (SD) of SPPB is 2.6 points; the correlations between repeated measures of SPPB are estimated at 0.5; the correlations of baseline LEM and baseline handgrip strength with SPPB measures are estimated at 0.5); c) a treatment effect of 0.5, 0.75, and 1 SPPB point(s) is achieved at weeks 6, 12, and 26, respectively; d) the missing measurements are at random at a magnitude of 15%; and e) the statistical model used to calculate study power is mixed model repeated measures (MMRM), incorporating the comparison between the study groups of the outcome adjusted means estimates at Week 26 for SPPB as derived from the treatment by visit interaction fixed effect tested.

The MMRM included visit (six, 12, and 26 weeks) and cohort (PLX-PAD and placebo) according to the assumption described above. As the target time point was 26 weeks, the model included the interaction factor between cohort (i.e. treatment assignment) and visits (i.e. different timepoints). The model contains information from other time points. Using more information from other time points normally yield a smaller sample size.

In conclusion, for the primary endpoint (SPPB value at week 26), a total sample size of 240 subjects will provide power of approximately 88% for the detection of a treatment effect of 1 SPPB point at a two-sided α level of 5%, assuming the correlations of baseline LEM and baseline hand grip strength with SPPB is 0.5.

Primary endpoint analysis. The intent-to-treat (ITT) analysis set serves as the primary analysis set for efficacy evaluation and inference of the mean 26-week SPPB scores.

SPPB missing data will be handled by implementing the multi-imputation (MI) procedure. The week 26 SPPB scores will be analyzed using an analysis of covariance (ANCOVA) model (SAS MIXED procedure) to derive treatment effects. The model will include: treatment group, CGR (country/geographical region), type of surgery, severity of muscle injury, sex, age category, and baseline LEM. Treatment effects, 95% confidence intervals, and p-values will be calculated using the SAS MIANALYZE procedure.

Secondary endpoints statistical consideration. For the analysis of the secondary efficacy endpoints, a step-down sequential testing procedure will be used to control the overall Type 1 error at 0.05. With this procedure, primary and secondary efficacy endpoints will be evaluated for statistical significance based on a pre-specified sequence for interpretation (primary: SPPB at week 26; secondary: Hip Abduction Strength, LEM change from baseline to week 52, lean body mass of the injured leg at week 26 (DEXA), SPPB score at Week 52, and all-cause mortality rate).

Trial organization and oversight. The HIPGEN study is funded by the European Union under the Horizon 2020 programme (grant number 779293). The HIPGEN consortium is coordinated by Charité-Universitätsmedizin Berlin and includes the multinational partner institutions (see Acknowledgements).

There are two external advisory boards and a Data Safety Monitoring Board composed of internationally renowned experts (see Acknowledgements), who are consulted regularly to oversee quality and status of the HIPGEN trial. Yearly meetings are held during which all partners gather to discuss study status, problems, and solutions in the consortium-wide forum. Day-to-day management is performed at the sites by the CRO ICON. Video conferences are held weekly between the coordinator (Charité), sponsor (Pluristem Ltd), InnActa, and other consortium members as necessary if specific topics require additional input.

Discussion

In the clinical setting, skeletal muscle injuries can occur as the result of traumatic events,[34,35] or due to surgical exposure, such as during arthroplasty implantations.

The main aim of FNF treatment is quick rehabilitation. However, despite modern perioperative care strategies, such as those presented in the National Institute for Health and Care Excellence guidelines,[36] there has not been a significant improvement in the high morbidity and mortality rates of FNF patients in the past decades.[37–39]

Such injuries may lead to fatty atrophy and volumetric muscle loss.[9,10] To date, no therapy has been introduced into clinical standard of care that is capable of restoring muscle tissue and function.

The HIPGEN trial assesses a biological solution for improved mobility after FNF arthroplasty by positively influencing the restoration of muscle function. We hypothesize that the proposed therapy will improve mobility and reduce mortality after FNF arthroplasty, and could therefore contribute to the European initiative to promote healthy ageing.

Take home message

- Hip fractures in the elderly are a leading public health concern.
- The need for early mobilization after fracture treatment is widely accepted to prevent adverse events.
- The HIPGEN project evaluates the efficacy and safety of intramuscular administration of PLX-PAD cells to improve the recovery after hip fractures.

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Data sharing:

- The datasets generated and analyzed during the current study are not publicly available due to the blinding of the study, but will be available from the corresponding author on reasonable request after publishing the study results. Dissemination of study results is performed by members of the study group at international conferences and meetings, as well as by the HIPGEN partner IOF, which has a vast network of international daughter organizations and also disseminates results on social media and its own meetings.

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The HIPGEN study during the COVID-19 pandemic:

When the COVID-19 outbreak was revealed to be even more serious in all countries in 2020, recruitment and clinical research activities stopped in almost all the sites. A large percentage of the research staff was in home office in many sites and the medical staff was dedicated to deal with the clinical burden of the COVID pandemic. For certain periods, only COVID-19 related research projects were allowed to be active in nearly all sites. Furthermore, patients weren't allowed or denied arrival to follow up visits and due to logistic problems, on site monitoring and sponsor visits halted. With the ongoing pandemic situation and its state specific regulations and alterations, the follow-up visits of the enrolled patients were adopted as phone visits, home visits and with further easing as in-house visits applying the rules of the actual versions of the state- and site-specific Infection Protection Acts. However, applying all these measures to counteract the impact of the pandemic, the HIPGEN study has managed to keep actively recruiting patients, a part from period in spring 2020, and is on its way to meet its recruitment target of 240 patients.

Ethical review statement:

- The study was approved by the regulatory authorities and the Ethics Committees (EC)/Institutional Review Boards (IRB) in Germany, UK, US, Denmark, Israel, and Bulgaria. Written informed consent is collected from all patients, and the study was registered under ClinicalTrials.gov with the identifier NCT03451916. All study procedures are in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

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