1. TITLE PAGE

CLINICAL STUDY REPORT

PLX-PAD

A 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 (HF)

Protocol Number:	PLX-HF-01
Name of Test Product:	PLX-PAD: Allogeneic *ex vivo* expanded placental stromal cells
Indication:	Treatment of muscle injury following hip arthroplasty
Phase:	III
Methodology:	Multicenter, randomized, double-blind, placebo-controlled study
First Patient Enrolled:	05 August 2018
Last Patient Enrolled:	11 November 2021
Date of Report:	18 July 2023
Sponsor:	Pluri Biotech Ltd. Matam Park, Building 05, Haifa 3508409 Israel Telephone: +972-74-710-8600
Responsible Medical Officer:	Nitsan Halevy, MD, Chief Medical Officer Matam Park, Building 05, Haifa 3508409, Israel e-mail: nitsan.halevy@Pluri-biotech.com Telephone: +972-74-710-7116
Good Clinical Practice (GCP) Statement:	This study was performed in compliance with the study protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Consolidated Guideline E6 of GCP, and local regulatory requirements.

2. SYNOPSIS

Name of Company:
Pluri Biotech Ltd.

Name of Finished Product:	**Name of Active Ingredient:**
PLX-PAD	Allogeneic *ex vivo* expanded placental stromal cells

Title of Study:
A 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 (HF)

Investigators and/or Study Centers:
The study was conducted in a total of 20 sites in Bulgaria, Denmark, Germany, Israel, the United Kingdom (UK), and the United States of America (USA). A detailed list of the study sites and Principal Investigators is provided the appendices of the clinical study report (CSR).

Publication (reference):
T. Winkler, M. L. Costa, R. Ofir, O. Parolini, S. Geissler, H-D. Volk, C. Eder, On behalf of the HIPGEN Author Consortium. HIPGEN: a randomized, multicentre Phase III study using intramuscular PLacenta-eXpanded stromal cells therapy for recovery following hip fracture arthroplasty: A study design. Bone Jt Open 2022;3-4:340–347. doi: 10.1302/2633-1462.34.BJO-2021-0156.R1

Studied Period:	**Phase of Development:**
05 August 2018 – 26 October 2022	Phase III

Objectives:
The objectives of this study were to assess the efficacy, safety, and tolerability of PLacental eXpanded-Peripheral artery disease (PLX-PAD) intramuscular (IM) administration for the treatment of muscle injury following arthroplasty for HF.

Methodology:
This was a Phase III, multinational, randomized, double-blind, placebo-controlled study, designed to assess the efficacy, safety, and tolerability of IM administration of allogeneic PLX-PAD cells for the treatment of muscle injury following arthroplasty for HF.

Potential patients were to be assessed for study eligibility before the emergency surgery for HF. After being found eligible, patients were to be randomized using a 1:1 allocation scheme to either 150 million PLX-PAD cells or to placebo treatment. Patients were to undergo hemi-arthroplasty (HA), or total hip arthroplasty (THA) planned within 48 hours of admission and up to 72 hours following fracture. During the surgical procedure, patients were to receive the investigational product (IP) (PLX-PAD/placebo) in accordance with the study arm to which they were randomized.

Following initial hospitalization for surgery, all patients were to be treated by standard geriatric rehabilitation per local practice. Patients were to be provided with supplemental vitamin D and calcium as per local practice. Patients were to be routinely followed- up for pain control during the study. In case of suspected malnutrition, the patients were to be referred to a dietician. In order to minimize potential allergic/hypersensitivity reactions to study treatment, patients were to be pre-medicated with a second- or third-generation antihistamine before the start of the HA/THA surgery (for 24 hours coverage).

The main study period was planned to last from screening to 52 weeks post-treatment, and to include the following 4 stages:

1. Screening and pre-surgery time
2. Surgery and treatment with PLX-PAD or placebo (Day 0)

3. Hospital follow-up period until hospital discharge
4. Follow-up period up to 52 weeks following study treatment administration

The following study visits were to be included in the main study period: screening, Day 0 (treatment and surgery day), Day 1, Day 5, Week 6, Week 12, Week 26, and Week 52.

The main study period was to be followed by a long-term safety follow-up period, between Week 52 and Week 104 (last study visit). Only survival and quality of life (QoL) data, serious adverse events (SAEs) assessed by the Investigator as related to study treatment, and new malignancy adverse events (AEs) were to be collected during this period.

The expected duration of the study for each patient was 104 weeks. After the last patient had completed the Week 26 visit, data up to Week 26 were to be frozen/soft-locked for all patients up to and inclusive of the Week 26 visit, including all data for early terminated and screen failure patients, and unblinded efficacy and safety analyses were to be performed. Study site personnel (blinded), site monitors, and patients were to remain blinded until Week 104.

Recruitment time was expected to last 36 months.

Number of Patients (Planned and Analyzed):

Approximately 240 patients were planned to be randomized into this study.

A total of 240 patients were enrolled in the study, of which 120 patients were randomized to the PLX-PAD arm, and 120 patients were randomized to the placebo arm.

Diagnosis and Main Criteria for Inclusion:

The study population was to consist of patients suffering from low-energy trauma intracapsular neck of femur fracture, treated by arthroplasty.

A complete list of inclusion and exclusion criteria is provided in the main body of the CSR.

Test Product, Dose and Mode of Administration, Batch Number(s):

Following implantation of the femoral stem and suturing of the gluteus medius (GM) muscle, and prior to suturing of the iliotibial tract, PLX-PAD was to be administered to the affected incised GM muscle, using an off-the-shelf needle via 10 IM injections, 1.5 mL each (a cumulative volume of 15 mL).

The test product administered in this study was PLacental eXpanded-Peripheral artery disease (PLX-PAD). PLX-PAD was to be provided as a frozen cell dispersion in 6 mL crystal vials containing 150 million PLX-PAD cells (at a cell concentration of 10 million cells/mL), in a solution containing 10% dimethyl sulfoxide (DMSO) (v/v) and 5% human serum albumin (HSA) (w/v) in PlasmaLyte.

Prior to treatment, PLX-PAD was to be thawed and transferred to syringes for administration.

A by-patient list of PLX-PAD batches used in the study is provided in Appendix 16.1.6 of the CSR.

Reference Therapy, Dose and Mode of Administration, Batch Number(s):

Following implantation of the femoral stem and suturing of the GM muscle, and prior to suturing of the iliotibial tract, placebo was to be administered to the affected incised GM muscle, using an off-the-shelf needle via 10 IM injections, 1.5 mL each (a cumulative volume of 15 mL).

Placebo was to be provided as a frozen solution comprising 10% DMSO (v/v), 5% HSA (w/v), and PlasmaLyte, without cells.

Prior to treatment, placebo was to be thawed and transferred to syringes for administration.

A by-patient list of placebo batches used in the study is provided in Appendix 16.1.6 of the CSR.

Duration of Treatment:

Each patient was to be administered a single IM injection of either PLX-PAD or placebo on Day 0.

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint of the study was the Short Physical Performance Battery (SPPB) score at Week 26.

The secondary efficacy endpoints of the study were the following:

- Hip abduction strength (HAS) of the injured leg at Week 26
- Change from baseline to Week 26 in lower extremity measure (LEM) (retrospective collection of pre-fracture LEM at Day 5)
- All-cause mortality rate

The study also included additional exploratory efficacy endpoints (Section 8.3).

Safety and Tolerability:

- AEs and SAEs
- Safety laboratory data (hematology and biochemistry)
- Vital signs
- Physical examination findings
- Proportion of patients (%) who prematurely discontinued from the study
- Proportion of patients (%) who prematurely discontinued from the study due to AEs

Pharmacokinetics:

Not applicable.

Statistical Methods:

Primary and secondary efficacy and key safety analyses were to be performed after the last patient had completed the Week 26 follow-up visit, and relevant electronic case report form (eCRF) pages in the study database had been locked.

Except where otherwise noted, all statistical analyses were to be performed using SAS® version 9.2 (or higher) (SAS Institute, Cary, North Carolina).

Except where otherwise noted, all statistical tests were to be two-sided. The type 1 error rate was to be controlled at the 0.05 level of probability for the primary endpoint and key secondary endpoints. All other p-values were to be reported with no correction for multiplicity.

Excluding cases in which specific imputation methods were used, continuous variables were to be summarized with number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum values displayed. Categorical data were to be summarized with number of non-missing observations as counts and percentages.

The following analysis sets were planned for the statistical analyses in this study:

Intent-to-treat (ITT) analysis set: All randomized patients. In this population, treatment was to be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. The ITT comprised all 240 patients who were randomized to one of the two study arms (PLX-PAD or placebo; 120 patients in each arm).

Modified intent-to-treat (mITT) analysis set: All patients in the ITT analysis set who received the study treatment injection and had at least one post-baseline non-missing primary efficacy observation. The mITT included 199 patients (97 in the PLX-PAD arm and 102 in placebo).

Per-protocol (PP) analysis set: All patients who were included in the mITT and did not have specific major protocol deviations. The PP included 199 patients (97 in the PLX-PAD arm and 102 in placebo).

Safety (ST) analysis set: All patients who had been randomized and received the study treatment administration according to treatment actually administered. The ST included 233 patients (116 in the PLX-PAD arm and 117 in placebo).

Patients' data in the different analysis sets, including data of patients who withdrew from the study and patients who discontinued study treatment, were to be summarized using descriptive statistics.

Determination of sample size: This study was powered to demonstrate the superiority of PLX-PAD as compared to placebo treatment in the primary endpoint and in the secondary endpoints of HAS of the injured leg at Week 26 and change from baseline to Week 52 in LEM.

A full description of the sample size determination is provided in the main body of the CSR.

Primary efficacy endpoint: The ITT was to serve as the principal analysis set for the primary efficacy endpoint and the description of patients' disposition.

Full details on handling of missing data in the primary endpoint analysis are provided in the statistical analysis plan (SAP). Briefly, there were several scenarios that could lead to early termination and missing data. For the primary endpoint analysis, these were:

- For patients who terminated the study due to death or other AE, all their missing SPPB scores forward were to be set as failure (SPPB score = 0)
- For all other early termination patients, SPPB was to be imputed by the multiple imputations (MI) procedure as detailed in the SAP
- For patients with partial results for the SPPB, with missing overall score value, their SPPB score value was to be assigned by the Medical Director based on the reported reasons for missing values and recorded in a note to file (NTF) prior to database lock (DBL) and unblinding

Patients with a missing SPPB overall score were to have their missing SPPB score imputed based on the missing at random (MAR) assumption, which was to be imputed by the MI approach, using a linear regression model as described in the SAP.

The robustness of the principal analysis of the primary endpoint was to be explored employing the following:

- Sensitivity analyses not related to missing data, including analyses of the mITT and PP sets, primary efficacy endpoint analysis without baseline LEM, and primary efficacy endpoint analysis without covariates
- Sensitivity analyses related to missing data, including mixed measures repeated model (MMRM) analyses in the mITT and PP sets, analyses assuming missing not at random (MNAR) in the mITT and PP sets, analysis using the SPPB last observed value (LOV) up to Week 26, analysis of MNAR missingness mechanism as percentage grid from MI of active arms in the ITT, analysis of MNAR missingness mechanism using shift values range from MI of active arms to achieve p-value >0.05 in the ITT

Planned sub-group analyses to the primary efficacy endpoint included sub-grouping based on the following categories: age (dichotomized by the overall median at baseline); sex; USA and non-USA patients; country; glycosylated hemoglobin (HbA_{1c}): ≤ or >6.4%; baseline LEM: ≤ or > median; surgery type: HA or THA; and severity of muscle injury at screening: mild, moderate, or severe.

Secondary efficacy endpoints: For the analysis of the secondary efficacy endpoints, a step-down sequential testing procedure was to be used to control the overall type 1 error at 0.05.

If at any point in the sequence statistical significance was not met, subsequent endpoints in the sequence could not be deemed statistically significant, although nominal p-values were to be reported and considered descriptive.

All secondary endpoint analyses were to be conducted on the ITT set.

Exploratory efficacy analyses: All exploratory endpoint analyses were to be conducted on the mITT population. Details on these analyses are provided in the SAP.

Safety analyses: The ST was to be used for evaluation of safety data up to Week 52, as well as for evaluation of data on treatment-related SAEs and malignancy AEs/SAEs recorded up to Week 104. Safety data analyzed was to include AEs, hematology and biochemistry laboratory tests, vital signs, physical examinations, and premature discontinuation from the study. A description of the statistical analyses for these safety variables is provided in the body of the CSR.

Changes in the planned analyses: A list of planned analyses that were not performed (including reason for not having been performed), as well as a list of post hoc analyses are provided in the main body of the CSR. Statistical procedures used for the post hoc analyses are described in the main body of the CSR.

Summary and Conclusions:

Early termination of the study: Following the completion of the primary efficacy analysis, in which it was determined that the PLX-HF-01 study did not meet its primary endpoint, a decision was made on 02 August 2022 to early terminate the study, and thus, the study was terminated at the end of its main period (52 weeks post-treatment). All active patients who had not completed the Week 52 visit by the time this decision was made were encouraged to complete this visit as per the study protocol. The study did not continue to the completion of the Week 104 visit, and therefore, the ability to assess Week 104 safety data was impaired, with a total of 73 patients in the study not reaching the Week 104 visit. To minimize this impact, all active patients who had completed the Week 52 visit and had not completed the Week 104 visit were asked to attend a phone visit, during which relevant safety data were collected and recorded. Of note, although the primary data analysis showed that the primary endpoint of the study had not been met, it also showed that PLX-PAD was well tolerated.

Changes in the conduct of the study due to the COVID-19 pandemic: A list of modifications to the conduct of the study due to the COVID-19 pandemic is provided in the main body of the CSR.

Patient Characteristics at Study Entry:

Overall, the demographic parameters and baseline characteristics of patients recruited to this study were comparable between the two arms. Most of the patients (62.1%) were above 75.0 years of age (median 79.0 years), with a larger proportion of females (70.8%).
Most patients had Garden IV (66.5%) severity of initial hip displacement, which was comparable between the two study arms. The muscle injury was evaluated (based on myoglobin test levels measured at screening and on Day 1) as mild for the majority of patients (85.3%). The most common surgical procedure was THA (58.1%) and most of the patients (67.9%) had cementless fixation.

Summary of Efficacy:

The primary endpoint of this study, the SPPB score at Week 26, was not significantly different between the two study arms (6.873 in the PLX-PAD arm and 7.039 in placebo). Results of sensitivity analyses to the primary endpoint, both related and unrelated to missing data, aligned with this observation. Likewise, consistent results were shown in various tested sub-groups, with no statistically significant differences between the two study arms. These results were further supported by a series of exploratory and post hoc analyses testing the SPPB score at Week 52 and the SPPB sub-scores at Week 26.

These findings, however, should be assessed with caution due to the fact that the study population was elderly and had a high rate of comorbidities. In this type of population, performance-based analyses such as the SPPB score used in the study's primary objective may be limited in their ability to detect potential changes in the patients' function as impacted by muscle strength and volume. Thus, the primary endpoint in this study may not be an optimal measure of PLX-PAD potential efficacy in the study population.

Summary of Pharmacokinetics:

Not applicable.

Conclusions:

Although the primary and secondary efficacy endpoints, were not met, several exploratory and post hoc endpoints suggest a beneficial effect of PLX-PAD compared to placebo in the study population,

with a significant increase in CFR HAS in both injured and uninjured legs at Weeks 26 and 52 in PLX-PAD-treated patients, compared to those treated with placebo, supported by a trend for conservation of appendicular LBM in the injured leg for PLX-PAD patients versus an observed loss for placebo-treated patients. The safety results of the current study are consistent with the safety profile established for PLX-PAD in previous studies (including Phase I, Phase II, and Phase III studies), showing that PLX-PAD is well tolerated, and indicating no new safety risks in this study population.

Future work is required to better identify potential functional correlates of this effect and characterize the patient population which may benefit from this increase in muscle strength.

Date of the Report: 18 July 2023