# COVER SHEET

## CLINICAL STUDY REPORT SYNOPSIS

**EudraCT Number:** 2015-005532-18

**Protocol Number:** PLX-CLI-03

A Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel- Group Phase III Study to Evaluate the Efficacy, Tolerability and Safety of Intramuscular Injections of PLX-PAD for the Treatment of Subjects with Critical Limb Ischemia (CLI) with Minor Tissue Loss who are Unsuitable for Revascularization (PACE Study)

**Early Study Termination:** Following review of interim analysis data by an independent data monitoring committee, it was concluded that the study was unlikely to meet its primary efficacy endpoint. The decision was taken to terminate the study early on the basis of futility and an early termination notification was issued on December 14th 2020. It should be noted that there were no specific safety concerns regarding the study, and that the study drug was well tolerated.

# 1. TITLE PAGE

## CLINICAL STUDY REPORT

## A Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Phase III Study to Evaluate the Efficacy, Tolerability and Safety of Intramuscular Injections of PLX-PAD for the Treatment of Subjects with Critical Limb Ischemia (CLI) with Minor Tissue Loss who are Unsuitable for Revascularization (PACE Study)

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|---|---|
| **Protocol Number:** | PLX-CLI-03 |
| **Name of Test Drug/Product:** | PLX-PAD, allogeneic *ex vivo* expanded placental mesenchymal-like adherent stromal cells |
| **Indication:** | CLI with minor tissue loss in patients unsuitable for revascularization |
| **Phase:** | Phase III |
| **Methodology:** | A Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study |
| **First Subject Enrolled:** | 27 September 2017 |
| **Last Subject Enrolled:** | 16 November 2020 |
| **Date of Report:** | 10 January 2022 |
| **Sponsor:** | Pluristem Ltd.<br>MATAM Park, Building Number 5, Haifa 3508409, Israel<br>Telephone: +972-74-710-7116<br>Email: nitsan.halevy@pluristem.com |
| **Responsible Medical Officer:** | Nitsan Halevy, MD<br>Telephone: +972-74-710-7116<br>Email: nitsan.halevy@pluristem.com |
| **Good Clinical Practices (GCP) Statement:** | This study was conducted in compliance with the 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. |

**Confidentiality Statement**
The information contained herein is strictly confidential and the proprietary property of Pluristem Ltd. and any unauthorized use or disclosure of such information without the prior written authorization of Pluristem Ltd. is expressly prohibited.

# APPROVAL SIGNATURE PAGE

**APPROVED BY:**

| Nitsan Halevy, MD | Nitsan Halevy | 2022-06-07 |
|---|---|---|
| Chief Medical Officer | Signature | Date |

# 2. STUDY SYNOPSIS

| **Name of Company:** | **Name of Finished Product:** | **Name of Active Ingredient:** |
|---|---|---|
| Pluristem Ltd. | PLX-PAD | Allogeneic *ex vivo* expanded placental mesenchymal-like adherent stromal cells |

**Title of Study:**

A Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Phase III Study to Evaluate the Efficacy, Tolerability and Safety of Intramuscular Injections of PLX-PAD for the Treatment of Subjects with Critical Limb Ischemia (CLI) with Minor Tissue Loss who are Unsuitable for Revascularization (PACE Study)

**Investigators and/or Study Centers:**

The study was conducted in 42 sites in the United States and in Europe. A list of active sites and site-leading Investigators is provided within the clinical study report (CSR).

**Publication (reference):**

PLX-PAD Cell Treatment of Critical Limb Ischaemia: Rationale and Design of the PACE Trial: https://pubmed.ncbi.nlm.nih.gov/30686676.

| **Studied Period:** | **Phase of development:** |
|---|---|
| 27 September 2017 to 4 February 2021 | Phase III |

**Objective:**

The objective of the study was to evaluate the efficacy, tolerability, and safety of local intramuscular (IM) injections of PLX-PAD in CLI subjects unsuitable for revascularization.

**Methodology:**

This was a randomized, placebo-controlled, parallel-group, multicenter, Phase III study conducted in CLI subjects with minor tissue loss who were unsuitable for revascularization.

Entire Study Duration: End of Study was defined as 12 months after the first scheduled treatment visit of the last randomized subject, or the time at which 82 primary endpoint events had accumulated, whichever was later (defined here and after as "End of Study").

Individual Subject Study Participation: Following a screening period of up to five weeks, subjects were to be randomized using a 2:1 ratio to receive PLX-PAD $300\times10^6$ cells or placebo, respectively. Subjects were to receive the assigned treatment twice, 60 days apart. All subjects were to be followed up until the End of Study or until completing 36 months of follow-up – the earlier of the two (defined for each subject as the "Termination Visit"). Hence, the study participation for a particular subject was to range between 12 to 36 months.

Study visits were to be conducted every month up to Month 6, then every three months until Month 12, and for subjects followed for more than 12 months, every four months until the subject's Termination Visit.

Follow-up visits were to include clinical assessments of the limb ischemia via ischemic lesions size and ischemic pain, as well as subjects' quality of life (QoL) (via health-related and disease-related questionnaires) and physiologic parameters (ankle brachial index [ABI], toe brachial index [TBI], transcutaneous oxygen pressure [$TcPO_2$], and/or other non-invasive measurement of perfusion [sub-



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study]). In addition, safety assessments including adverse events (AEs), physical examination, vital signs, and laboratory tests were to be monitored during the study.

Additional laboratory tests such as cytokine levels, T-cell activation, messenger ribonucleic acid (mRNA), circulating endothelial cells (CEC), endothelial progenitor cells (EPC), and diabetes tests were to be performed for research purposes in subsets of study subjects.

All subjects were to receive PLX-PAD/placebo in addition to best standard of care according to local medical practices, including control of cardiovascular risk factors, statins, anti-platelet drugs (unless on chronic anticoagulation therapy, or if contra-indicated), wound care management, and analgesics, as appropriate.

**Number of Subjects (Planned and Analyzed):**

Number of subjects planned: 246-300 subjects

Number of subjects enrolled: 213 subjects

**Diagnosis and Criteria for Inclusion and Exclusion:**

Inclusion Criteria:

Subjects had to meet all of the inclusion criteria listed below to be eligible for inclusion in the study:

1. Adult male or female subjects between ages 45-99 years of age at the time of screening.
2. Subjects with a diagnosis of peripheral artery disease (PAD) due to atherosclerosis at the stage of CLI, with minor tissue loss from arterial disease, up to the ankle level (the line between the top of the two malleoli) (black toe due to CLI was acceptable if not infected).
3. Total area of ischemic lesions $\leq$20 $cm^2$ (not including black toes).
4. Total area of ischemic lesions in the heel $\leq$10 $cm^2$.
5. Ankle pressure (AP) $\leq$70 mmHg or toe pressure (TP) $\leq$50 mmHg in the index leg.

   (If a subject had ABI >1.4 or both AP and TP were not measurable or not reliable, inclusion could be based on $TcPO_2 \leq$30 mmHg.)
6. Subjects unsuitable for revascularization (by any method) in the index leg based on unfavorable risk-benefit assessment of a multidisciplinary team including a vascular surgeon, and an interventionist/endovascular specialist (a vascular surgeon, angiologist/cardiologist/internist, interventional radiologist), and, if relevant, an anesthesiologist, confirmed once during the screening period. Unsuitability to revascularization was based on any of the following:
   - Anatomic considerations as: inappropriate target artery, diffuse/extensive tibial and/or peroneal artery lesions, inadequate distal run-off.
   - Technical considerations: inappropriate bypass conduit.
   - Failed revascularization (with persistence of CLI as defined in the clinical study protocol).
   - Medical considerations: subject's comorbidities.
7. Ischemic lesions in the index leg had to be not closed during the screening period, nor significantly worsened.



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8. Ischemic ulcers in the index leg had to be without tendon or bone exposure during the screening period unless the exposure was secondary to a minor amputation and there were no signs of osteomyelitis as per clinical assessment and imaging.
9. Subjects under treatment for cardiovascular risk factors: hypertension, hyperlipidemia, diabetes, in accordance with applicable guidelines, in order to achieve their stabilization. Concomitant therapy had to include a statin (or other lipid lowering drugs as part of standard of care) and an anti-platelet agent (e.g., clopidogrel, aspirin, etc.) for at least two weeks prior to randomization as part of standard of care (unless contra-indicated or unless subject was under chronic oral anticoagulation). Subjects had received recommendations on lifestyle changes (including smoking cessation) prior to randomization.
10. Women of childbearing potential had to have a negative serum pregnancy test at screening and had to be willing to use at least one highly effective birth control method throughout the study:
    a. Oral/intravaginal/transdermal combined estrogen and progestogen containing hormonal contraception for at least three months prior to screening.
    b. Oral/injectable/implantable progestogen-only hormonal contraception for at least three months prior to screening.
    c. An intrauterine device or intrauterine hormone-releasing system.

Any female subject who was surgically sterile, or with bilateral tubal occlusion, or whose partner was vasectomized, or who reliably applied sexual abstinence or who was postmenopausal (two years without menses) was considered not of childbearing potential.

11. Subjects understood, agreed, and provided informed consent. Subjects had to give written informed consent before any assessment was performed
12. For diabetic patients: under treatment with glucose lowering agents according to acceptable international guidelines.

Exclusion criteria:

Subjects with any one of the exclusion criteria listed below were not eligible for the study:

1. Non-atherosclerotic PAD (eg, Buerger's disease [thromboangiitis obliterans], Takayasu's arteritis, etc.).
2. CLI with major tissue loss (Rutherford Category 6) in either leg.
3. Evidence of active infection in either leg (eg, cellulitis, osteomyelitis). If there was clinical suspicion of osteomyelitis, imaging per local medical practice was to be performed. If a subject had osteomyelitis within the last three months, recovery was to be determined by the Investigator, supported by mandatory imaging as per local medical practice.
4. Subjects having undergone surgical revascularization or major amputation in either leg less than one month prior to screening, or endovascular revascularization or minor amputation less than two weeks prior to screening.
5. Planned or potential need for major/minor amputation or any revascularization of either leg during the screening period and up to one month following randomization according to Investigator's or treating physician judgment/decision.

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6. Aortoiliac stenosis or common femoral artery stenosis ≥70%, or otherwise suspicion of inadequate inflow to the index leg up to three months prior to screening by any imaging modality.
7. Current evidence or sign supporting an assessment of life expectancy of less than six months.
8. Stroke or acute myocardial infarction/unstable angina within three months prior to randomization.
9. Severe congestive heart failure symptoms (New York Heart Association [NYHA] class III-IV) at screening.
10. Life-threatening ventricular arrhythmia - except in subjects with an implantable cardiac-defibrillator at screening.
11. Uncontrolled severe hypertension during screening period.
12. Diabetes mellitus with glycosylated hemoglobin (HbA1c) >10% at screening.
13. Current or history of proliferative retinopathy (for all known diabetic subjects there was to be no evidence of proliferative retinopathy in a retinal examination performed within three months before First Screening Visit or during screening).
14. Known active untreated Hepatitis B virus or Hepatitis C virus infections at screening.
15. Subjects with known human immunodeficiency virus (HIV) infection, acquired immunodeficiency syndrome (AIDS), severe uncontrolled inflammatory disease or severe uncontrolled autoimmune disease (e.g., ulcerative colitis, Crohn's disease, etc.).
16. Preexisting significant coagulopathies that put a subject at an increased risk of blood clotting or bleeding according to the Investigator's judgment.
17. Subjects under chronic anticoagulant therapy taking warfarin with international normalized ratio (INR) >2 or treated with Direct Oral Anticoagulants, for atrial fibrillation and/or prosthetic heart valves, and or thromboembolic events, unless this therapy could be safely discontinued or modified around the time of PLX-PAD/placebo injections based on the study Investigator's discretion.
18. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3×upper limit of normal (ULN). Subjects with higher levels could be included if the condition associated with the increase in those liver enzymes was known and was considered clinically stable.
19. Subjects on renal replacement therapy or planned to start renal replacement therapy within three months of First Screening Visit.
20. Known history of drug or alcohol abuse in the past three years.
21. Subjects were at screening enrolled in, or had not yet completed a period of at least 30 days since ending another investigational device or drug trial(s), unless in long-term follow-up phase (in which there was no IP administration).
22. Current treatment with systemic steroids at a dose which was prednisone equivalent >5 mg/day, or topical steroids on the index leg.
23. Current use or use within 30 days prior to PLX-PAD treatment of wound dressing containing cells or growth factors like Apligraf®, or topical platelet derived growth factor.

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24. Planned use or use within 14 days prior to PLX-PAD treatment (V1) of hyperbaric oxygen therapy, prostanoids, pentoxifylline, cilostazole, spinal cord stimulation, or lumbar sympathectomy.
25. Exposure to allogeneic cell-based therapy in the past or exposure to autologous cell therapy in the last 12 months before screening.
26. Known allergies to any of the following: dimethyl sulfoxide (DMSO), human serum albumin, bovine serum albumin.
27. Known allergy to the antihistaminic drug selected by the site as pre-medication.
28. History of allergic/hypersensitivity reaction to any substance having required hospitalization and/or treatment with intravenous steroids/epinephrine, known allergy to more than three different allergens, or in the opinion of the Investigator the subject was at high risk of developing severe allergic/hypersensitivity reactions.
29. History of severe atopic disease (including but not limited to chronic urticaria, allergic reaction with respiratory symptoms requiring systemic steroids), or history of uncontrolled Asthma (Global Initiative for Asthma III-IV).
30. Pulmonary disease requiring supplemental oxygen treatment on a daily basis.
31. History of acute transfusion reaction.
32. History of autologous/allogeneic hematopoietic cell transplantation for bone marrow replacement or solid organ transplantation.
33. Active malignancy or history of malignancy within three years prior to screening except for successfully resected skin basal cell carcinoma or skin squamous cell carcinoma not located on the index leg.
34. Immunocompromised subjects for any reason, including immunosuppressive therapy, at screening.
35. In the opinion of the Investigator, subjects were unsuitable for participating in the study.
36. Chronic liver disease Child Pugh class B/C.

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

The PLX-PAD product was aseptically filled in cryogenic vials at a concentration of $20\times10^6$ cells/mL in a mixture containing 10% DMSO, 5% human serum albumin, and Plasma-Lyte.

PLX-PAD was to be administered to subjects in Arm 1 via 30 IM injections (0.5 mL each) delivered into the index leg. Each subject was to be treated twice, with an interval of 60 days between treatments.

PLX-PAD was to be administered in addition to best standard of care according to local medical practices.

The PLX-PAD batches used in the study included batches P150518R04, P150518R08, P250416R19, P250416R24, and P250416R25 from manufacturing process 4, and batches P021017R01, P021017R02, P021017R03, P150518R01, P150518R02, P150518R06, P150518R09-B, P150518R11, P180515R03, P180515R05, P180515R07, P250416R02, P250416R05, P250416R09, P250416R10,

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P250416R16, P250416R18, P250416R21, P250416R23, P250416R24-B, P250416R25-B, and P250416R26 from manufacturing process 3 (further details are provided in the body of the report).

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

Placebo was a solution comprised of 10% DMSO, 5% human serum albumin, and Plasma-Lyte, (without cells). Placebo was to be administered to Arm 2 subjects via 30 IM injections (0.5 mL each) delivered into the index leg. Each subject was to be treated twice with an interval of 60 days between treatments.

Placebo was to be administered in addition to best standard of care according to local medical practices.

The following placebo batch numbers were used in this study: PL110819, PL050319, PL131218, PL190618, PL211015, and PL231115.

**Duration of Treatment:**

Following a screening period of up to five weeks, subjects were to be randomized in a 2:1 ratio to receive PLX-PAD $300\times10^6$ cells or placebo, respectively. Subjects were to receive the assigned treatment (PLX-PAD /placebo) twice, 60 days apart (on Day 0 and on Day 60).

**Criteria for Evaluation:**

**Efficacy:**

Primary efficacy endpoint:

Time (days) from randomization to occurrence of major amputation of the index leg or death (amputation-free survival [AFS]).

Secondary efficacy endpoints:

- Time (days) from randomization to first occurrence of any of the following single events:
  - Major amputation of the index leg
  - Revascularization due to worsening of CLI in the index leg
  - All-cause mortality
- Time (days) from randomization to major amputation of the index leg
- Change from baseline in ischemic pain as assessed by numerical rating scale (NRS) at 6 months
- Proportion of subjects with complete healing of all ischemic lesions, i.e., ulcers and necroses in the index leg at 12 months
- Time (days) from randomization to occurrence of death

Exploratory endpoints:

In addition to the efficacy endpoints, this study had several exploratory endpoints and exploratory tests. A complete list of these endpoints and tests is provided in the main body of this CSR.

Post-hoc efficacy endpoints:

- AFS at 12 months

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- Analyses of poorly controlled diabetics (HbA1c > 6.4% sub-population), and the non-diabetic/well-controlled diabetic sub-population (HbA1c ≤ 6.4% sub-population)

**Pharmacokinetics:**

No pharmacokinetic evaluations were to be performed.

**Safety and Tolerability:**

Safety endpoints:

- AEs and Serious AEs (SAEs)
- Safety laboratory values
- Vital signs and electrocardiogram (ECG)
- Physical examination findings

Tolerability endpoints:

- Proportion of subjects (%) who prematurely discontinued from the study by reason of discontinuation and the time to withdrawal
- Proportion of subjects (%) who prematurely discontinued from the study due to AEs and the time to discontinuation due to AEs

**Statistical Methods:**

Randomization:

An eligible subject who signed an informed consent form was to be randomly allocated to treatment with PLX-PAD $300\times10^6$ cells or with placebo based on a randomization scheme employing a 2:1 assignment ratio using permuted blocks stratified by geographical region (Western Europe, Central/Eastern Europe, North America), total lesion area (low risk: measurable lesions <10 $cm^2$ or a single black toe to any extent versus high risk: any ischemic lesion with black toe to any extent or more than one black toe to any extent or measurable lesions ≥10 $cm^2$), and diabetes mellitus (yes, no).

Sample size rationale:

The power and the derived sample size for the study were estimated based on the following assumptions:

- Subjects would be randomized into the study using a 2:1 ratio to treatment with PLX-PAD $300\times10^6$ cells or with placebo, respectively.
- The expected placebo survival curve was modeled by a piecewise linear function defined by the survival probabilities of 0.65, 0.53625, and 0.48933 at Year 1, Year 2, and Year 3, respectively. These three survival probabilities correspond to assumed risk rates of 0.35, 0.175 and 0.0875 during successive years, i.e., the chance of having an event in a given year, given survival up to the beginning of that year is halved for each successive year. The estimate of AFS of 65% for the first year was based on reported outcomes of control groups in previously published studies in CLI patients who were not considered for revascularization. For the 2-year and 3-year estimates, public data of clinical trials showed that most of the events of major amputation or death occurred within the first six months after study start and that the risk of events remarkably declined afterwards, an observation



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further supported by epidemiological survey outcome of all CLI patients. Therefore, in this study's power analyses, it was assumed that the risk of events of major amputation or death in the control group would decrease by half from Year 1 to Year 2 and additionally by half from Year 2 to Year 3, providing the above listed estimates.

- The expected PLX-PAD survival curve was a piecewise linear function defined by the following three time points: 0.82, 0.7462, and 0.712621 for Year 1, Year 2 and Year 3, respectively. The corresponding constant hazard rates would be 0.1985 and 0.0943 during Years 1 and 2 respectively, and 0.0460 after two years. The assumption of risk reduction of approximately 50% in the PLX-PAD arm as compared to placebo treatment in the first year was based on the pooled data of the two Phase I studies previously conducted by the Sponsor that demonstrated an AFS rate of 85% at 1-year for PLX-PAD-treated subjects.
- To simplify power estimation, for sample size determination the log-rank test was used to non-parametrically compare the overall survival curves of the two treatments.
- For the power calculation it was assumed that subjects were to be accrued uniformly over two years and then followed for an additional one year past the accrual period.
- Some loss to follow-up was expected, with roughly exponential rates with theoretical median of five years for both arms. This corresponds to expected losses of 12.9% within one year of follow-up.

Based on these assumptions, the required number of primary endpoint events for achieving a power of 90% was 82. The expected number of subjects to be recruited was ~264. The final number of subjects to be recruited by End of Study would be at least 246, with a maximum of 300 subjects.

For sample size estimation, an alpha level of 0.0452 (O'Brien-Fleming) was to be used.

An interim analysis was planned when at least 50% of the information would be accrued, i.e., after half the required number of primary endpoint events had been observed. The interim analysis was to be performed at an alpha of 0.01 and was to include the primary efficacy endpoint, safety, and tolerability.

Based on the same assumptions, if at an interim analysis at least 45 primary endpoint events were observed, a power of at least 44.7% could be achieved with the originally assumed effect size of a 48.6% risk reduction, at a two-sided alpha level of 0.01. At such an interim analysis with a true effect size of a 60% risk reduction, the power of at least 78.9% could be achieved.

The purpose of the interim analysis was identification of overwhelming effect or futility of treatment.

Efficacy analyses:

*Significance Level and Multiplicity Adjustment*

The overall alpha level for this study was 0.05, with alpha level of 0.0452 for the primary endpoint, using two-tailed tests. One primary endpoint and five secondary endpoints were pre-defined in this study. Hence, at the End of Study analysis, there were a total of six comparisons for the primary and secondary endpoints. At the End of Study analysis, the hierarchical method for multiple endpoints testing for the secondary endpoints utilized the gate keeping approach, ensuring that the overall experiment-wise type-I error of 0.05 was preserved. If the principal analysis of the primary endpoint statistically significantly favored PLX-PAD treatment, then the first secondary endpoint was to be tested using the applicable two-sided alpha level. Otherwise, significance testing was to be conducted



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for exploratory purposes. This gatekeeping principle was followed for testing subsequent secondary endpoints.

The secondary endpoint analyses were conducted only at the End of Study. If the End of Study was to be carried out after a significant result for the primary endpoint at the interim analysis, the significance level for the secondary endpoints would be 0.05. All efficacy analyses were to pertain to the Intent-to-treat (ITT) analysis set, which served as the principal analysis set for inference.

*Primary Efficacy Endpoint*

For the primary endpoint of this study, mortality from all causes was to be considered as an event. The rules incorporated to derive this endpoint are provided in the main body of this CSR.

The principal analysis of the primary endpoint was to be conducted utilizing the baseline adjusted Cox's proportional hazards (PH) model (SAS® PROC PHREG). Covariates included in the model and the treatment indicator (dummy variable) are detailed in the main body of this CSR.

The Hazard Ratio (HR) and its 95% Wald confidence interval were to be reported for the size of the treatment effect. The Wald chi-square p-value for the treatment effect was to be the formal p-value for the primary endpoint analysis unless the PH assumption was found not to hold.

The time to event was to be presented using Kaplan-Meier plots.

Several sensitivity analyses (described in the main body of the CSR) were to be conducted to assess the robustness of the principal statistical analysis of the primary endpoint.

Additional details are provided in the Statistical Analysis Plan (SAP).

*Secondary and Exploratory Endpoints*

Details of specific statistical analyses to be conducted for the five secondary efficacy endpoints, as well as those for the exploratory endpoints and tests are provided in the SAP.

*Post-hoc Endpoints*

In general, the statistical methods used in the post-hoc analyses were similar to those used in the primary/secondary endpoint analyses. As the endpoints had not changed, the same methodology was used, except for the restricted mean survival time (RMST), which was added as an alternative method for analyzing the HR for time to event outcome analysis.

Safety and tolerability analyses

Safety and tolerability analyses were to include analysis of treatment emergent adverse events (TEAEs, defined as adverse events following treatment administration) with PLX-PAD versus placebo.

Analyses of safety laboratory parameters were to be performed using the changes from baseline to each treatment visit and to the last observed value. Shift analysis was also to be performed using the normal ranges classifications. Incidence (%) of subjects with potentially clinically significant (PCS) abnormal values was also to be presented.

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Vital signs were to be analyzed using the changes from baseline to each treatment visit and to last observed value. A summary table presenting the incidence (%) of subjects with PCS abnormal values was to be provided.

Tolerability analysis was to be based on the number and percent (%) of subjects who failed to complete 52 weeks of follow-up and presented by withdrawal reason. The time to withdrawal and time to withdrawal from the study due to AEs were to be presented using Kaplan-Meier plots.

Details of physical examinations, ECG analyses, and prespecified sub-group analyses are provided in the SAP.

**Summary and Conclusions:**

**Subject Characteristics at Study Entry:**

A total of 70 subjects were randomized in the placebo group and 143 in the PLX-PAD group (ITT population). The gender distribution of subjects at enrollment was comparable between the placebo and PLX-PAD arms, with 70% and 79% males, respectively. There were no women of childbearing potential included in the study and the mean age was 69.8 years. The majority of participants (205, 96.2%) were Caucasian. Subjects in the two arms had comparable mean height, weight, and body mass index (BMI) values.

**Summary of Efficacy**:

Primary endpoint: The primary endpoint of the study was not met, with a similar probability of occurrence of major amputation of the index leg or death found in the placebo and PLX-PAD arms (33.1% and 28.6%, respectively, log-rank p = 0.83). Additionally, there was no significant difference between the two arms according to the Cox's PH model (adjusted HR: 0.926, 95% CI: 0.527-1.625; Cox's Wald p = 0.79).

Secondary endpoints: In line with the primary endpoint analysis, the secondary endpoint analyses of the study found similar results, showing no significant difference between the placebo and PLX-PAD arms.

Similarly, none of the sub-group analyses for the secondary endpoints, as detailed in the main body of the CSR, showed a significant difference between the placebo and PLX-PAD arms.

**Summary of Safety:**

A total of 470 TEAEs were recorded in the PLX-PAD arm, with 100 (73.5%) subjects who experienced at least one TEAE. A total of 312 TEAEs were recorded in the placebo arm, with 57 (82.6%) subjects who experienced at least one TEAE.

The most frequent TEAEs in the PLX-PAD arms included skin ulcer in 32 (23.5%) subjects, extremity necrosis in 32 (23.5%) subjects, gangrene in 21 (15.4%) subjects, and ischemic limb pain in 20 (14.7%) subjects. The most frequent TEAEs in the placebo arm included skin ulcer in 18 (26.1%) subjects, gangrene in 14 (20.3%) subjects, extremity necrosis in 12 (17.4%) subjects, ischemic limb pain in 12 (17.4%) subjects, peripheral ischemia in 7 (10.1%) subjects, and sepsis in 7 (10.1%) subjects.

There were 64 (47.1%) subjects in the PLX-PAD arm and 41 (59.4%) subjects in the placebo arm with serious TEAEs, with a total of 147 and 76 serious TEAEs in the two arms, respectively. In the PLX-



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PAD arm the most frequent treatment emergent serious adverse events (TESAEs) by MedDRA Preferred Term (PT) were gangrene (in 13.2% of subjects), and extremity necrosis (in 12.5% of subjects). In the placebo arm, the most frequent TESAEs by PT included gangrene (in 18.8% of subjects), extremity necrosis (in 7.2% of subjects), sepsis (in 7.2% of subjects), and peripheral ischemia (in 5.8% of subjects).

There were a total of 47 (34.6%) subjects in the PLX-PAD arm and 33 (47.8%) subjects in the placebo arm, with a total of 89 and 73 with severe (grade ≥ 3 severity) TEAEs in the two arms, respectively. The most frequent severe TEAE in both arms was gangrene, followed by extremity necrosis the PLX-PAD arm, and by extremity necrosis and sepsis in the placebo arm.

A total of 16 (11.8%) subjects in the PLX-PAD and 9 (13.0%) subjects in the placebo arm experienced TEAEs related to treatment, with a total of 26 and 11 TEAEs related to treatment recorded in the two arms, respectively.

There was a comparable incidence of subjects with TEAEs that occurred within 72 hours from study treatment administration between the two arms (15.4% and 13.0% in PLX-PAD and placebo, respectively).

An overall 14 AEs in 13 subjects led to treatment discontinuation, including six AEs in six subjects on PLX-PAD, and eight AEs in seven subjects on placebo.

There were 29 deaths reported in this study, of which, four subjects died after screening and before randomization. The remaining 25 subjects died during the study, including one subject in the PLX-PAD arm who died after randomization and before dosing, 15 subjects (seven in the PLX-PAD arm and eight in the placebo arm) who died before Day 365 of the study, and nine subjects (eight in the PLX-PAD arm and one in the placebo arm) who died after Day 365 of the study.

Of expected TEAEs, there was a single case of abnormal breath odor in one subject in the PLX-PAD arm, which was determined by the Investigator as related to the study drug. There were no AEs of abnormal skin odor recorded in the study and no cases of allergic or hypersensitivity TEAEs reported in the study. The overall incidence of TEAEs classified as injection site reactions was 12.5% in the PLX-PAD arm and 10.1% in the placebo arm.

Of potential risks, there were four cases of malignancy (including one in the PLX-PAD arm and three in placebo); none was assessed as related to the study drug.

There were no TEAEs of unregulated angiogenesis reported in the study. There was one adverse event of proliferative diabetic retinopathy, which started 388 days following treatment with PLX-PAD, and one event of proliferative diabetic retinopathy recorded in a subject who was not treated with an investigational medicinal product (IMP).

Of events of particular interest, there were five subjects who experienced myocardial infarctions during the study and following treatment, including three subjects in the PLX-PAD arm and two in the placebo arm. All myocardial infarction events were assessed as non-related to study drug. All five subjects had multiple cardiac risk factors prior to participation in the study, providing an alternate causal role. There were five subjects who experienced events of cardiovascular accident, ischemic stroke, or cerebral infarction; all subjects were in the PLX-PAD arm, and all were assessed by the Investigator as not



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related to treatment. There were twelve subjects who died due to a cardiovascular cause, including eight subjects on PLX-PAD and four subjects on placebo.

There were no meaningful trends in change from baseline in hematology, blood chemistry, hepatic function, and urine chemistry laboratory parameters in either one of the two arms during the course of the study. Although some statistically significant changes between the two arms were observed, all of them were isolated findings with no accompanying trend.

There were no meaningful trends in any of the vital signs during the course of the study and no significant changes between the two arms in change from baseline during the course of the study.

There were no meaningful trends in total area of ulcers and total area of necrosis during the course of the study.

Statistically significant changes between the two arms were observed for mean changes from baseline in overall total area of ischemic lesions, with an increasing trend of decrease from baseline at Months 4, 5, 9, and 16 in the placebo arm, and an increase from baseline at these timepoints in the PLX-PAD arm.

There were no significant changes in mean baseline ECG heart rate and electrical interval durations between the two arms.

Overall, the safety and tolerability profile of PLX-PAD was as expected for study patient population.

**Date of the Report: 10 January 2022**

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