Title: A Randomized, International, Multicenter, Parallel Group, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Actovegin 12-Week Treatment Given First Intravenously and Subsequently Orally in Subjects With Peripheral Arterial Occlusive Disease Fontaine Stage IIB

NCT Number: NCT03469349

Protocol Approve Date: 19 February 2019

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

TAKEDA PHARMACEUTICALS PROTOCOL

A Randomized, International, Multicenter, Parallel Group, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Actovegin 12-Week Treatment Given First Intravenously and Subsequently Orally in Subjects With Peripheral Arterial Occlusive Disease Fontaine Stage IIB

Actovegin 12-Week Treatment Given First Intravenously and Subsequently Orally in Subjects With Peripheral Arterial Occlusive Disease Fontaine Stage IIB

Acronym Title: APOLLO

Phase 3

Sponsor:	Takeda Pharmaceuticals LLC, 2, bld.1, Usatchyova Str., Moscow 119048, Russian Federation		
Study Number:	Actovegin-3001		
IND Number:	Not Applicable	**EudraCT Number:**	2017-004741-24
Compound:	Actovegin		
Date:	19 February 2019	**Version/Amendment Number:**	Amendment 04

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
19 December 2017	Initial version	Not applicable	Global
02 April 2018	1	Not applicable	Russia
25 May 2018	2	Not applicable	Global
26 July 2018	3	Not applicable	Global
19 February 2019	4	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	All Countries
Safety reporting	PPD
Medical Monitor (medical advice on protocol and study drug)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

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1.2 APPROVAL

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

PPD

1.3 Protocol Amendment 04 Summary of Changes

This document describes the changes in reference to the Protocol incorporating Amendment No. 04. The primary reason for this amendment is to revise the number of participating sites and countries, clarify an inclusion criterion, clarify and correct specific study procedures and conditions, and include a list of adverse events of special interest (AESIs) in the protocol.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix E.

Changes in Amendment 04

1. Revised number of participating sites and countries.
2. Clarified inclusion criterion #11.
3. Clarified early discontinuation procedures.
4. Clarified that subjects should continue companion medications for peripheral arterial disease (PAD) and prevention of cardiovascular events.
5. Specified minimum infusion duration.
6. Corrected timing of oral treatment period.
7. Deleted instruction to collect incorrect demographic information.
8. Specified timing of height and weight assessments.
9. Clarified that questionnaires should be provided to patients in a language in which they are fluent.
10. Clarified fasting conditions and revised maximum blood volume collected.
11. Specified details of white blood cell count.
12. Added requirement to document lost or damaged tablets and defined the nature of returned tablets.
13. Added AESIs.
14. Clarified method of signing the informed consent.
15. Removed specific assessments from the Schedule of Study Procedures.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator. (Appendix B)

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical LLC	**Compound:** Actovegin	
Title of Protocol: A Randomized, International, Multicenter, Parallel Group, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Actovegin 12-Week Treatment Given First Intravenously and Subsequently Orally in Subjects With Peripheral Arterial Occlusive Disease Fontaine Stage IIB	**IND No.:** Not Applicable	**EudraCT No.:** 2017-004741-24
Study Number: Actovegin-3001	**Phase**: 3b	

Study Design:

This is a randomized, multicenter, parallel group, double-blind, placebo-controlled phase 3b study to evaluate the efficacy and safety of actovegin 12-week treatment given intravenously and subsequently orally in subjects with peripheral arterial disease (PAD) Fontaine Stage IIB.

A total of 366 subjects with PAD Fontaine Stage IIB will be enrolled in approximately 17 to 25 sites in 3 countries (Russia, Kazakhstan, and Georgia,).

The study will consist of a 1- to 2-week Screening Period, Randomization, 12-week Treatment Period, and 12-week Follow-up Period. The overall study duration will be 25 to 26 weeks.

Subjects will enter a 1- to 2-week Screening Period during which, the stability of the subject's condition will be verified, a diagnosis of PAD will be confirmed, and subjects with high variability in the absolute claudication distance (ACD) will be detected and excluded. For this purpose, 2 treadmill tests will be performed within a time interval of ≥1 week (ie, 7 days). Subjects having a change of more than 25% in the ACD during the Screening Period will be excluded.

Subjects with a confirmed history of stable intermittent claudication with symptoms that have been present continuously for at least 6 months at the time of Screening will be eligible for inclusion. A diagnosis of PAD (initial claudication distance [ICD] of <200 meters) will be confirmed by ultrasound color duplex imaging and treadmill test.

Eligible subjects will be randomized to receive either actovegin or placebo in a 1:1 ratio. The treatment period will include 2 weeks of intravenous (IV) infusions of actovegin (deproteinized hemoderivate) at a dose of 1200 mg/day, followed by 10 weeks of oral treatment in tablets at a dose of 1200 mg/day (two 200 mg tablets 3 times daily [TID]). Matched placebo (solution for infusion 0.9% NaCl and placebo tablets) will be used throughout the treatment period to maintain blinding. The overall treatment duration will be 12 weeks.

A 12-week follow-up period with no investigational medicinal product (IMP) treatment will follow the 12-week treatment period to examine sustained efficacy after treatment as well as safety once actovegin treatment has stopped.

During the active treatment period and follow-up period, patients will be allowed to receive other specific therapy for PAD with the exception of prohibited medications.

Primary Objectives:

The primary objective is to investigate the efficacy of actovegin for the symptomatic treatment of PAD Fontaine Stage IIB.

Secondary Objectives:

- To investigate the effect of actovegin in sustained improvement in claudication distance of subjects with PAD Fontaine Stage IIB.
- To investigate the effect of actovegin on patients' quality of life.
- To evaluate the safety of actovegin compared to placebo.

Subject Population: Male or female subjects with PAD Fontaine Stage IIB aged 40 to 75 years, inclusive.	
Number of Subjects: 183 subjects per treatment group Estimated total: Approximately 366 randomized subjects	**Number of Sites:** Approximately 17 to 25 sites in 3 countries (Russia, Kazakhstan, and Georgia)
Dose Level(s): **Actovegin ampoules** 400 mg/10 mL Solution for infusion 0.9% NaCl 250 mL 280 mL /1200 mg /intravenously / day for 2 weeks **Actovegin placebo ampoules** 0.9% NaCl /10 mL Solution for infusion 0.9% NaCl 250 mL 280 mL / intravenously / day for 2 weeks **Actovegin tablets** 200 mg Oral treatment 2 tablets 200 mg TID (1200 mg/day) for 10 weeks **Actovegin placebo tablets** Oral treatment 2 tablets TID for 10 weeks	**Route of Administration:** Actovegin IV infusions actovegin oral (tablets) Placebo (0.9% NaCl) IV infusions Placebo oral (tablets)
Duration of Treatment: 12 weeks (2 weeks of IV treatment and 10 weeks of oral treatment)	**Period of Evaluation:** Screening Period: 1 to 2 weeks Treatment Period: 12 weeks Follow-up Period: 12 weeks Overall study duration: 25 to 26 weeks

Main Criteria for Inclusion:

- Male or female subjects 40 to75 years of age, inclusive.
- The subject has a confirmed history of stable intermittent claudication with symptoms that have been present continuously for at least 6 months at the time of Screening.
- The subject has a diagnosis of PAD (Code I70.2 according to the international classification of diseases-10th revision) Fontaine Stage IIB confirmed by ultrasound color duplex imaging.
- The subject has a history of stable PAD therapy for at least 2 weeks before Screening and is not newly diagnosed with PAD.
- The subject has a history of stable smoking habits for at least 3 months before Randomization (Day 1)
- The subject has a resting Doppler ankle-brachial index of ≤0.9.
- The subject has intermittent claudication with ICD <200 meters.

Main Criteria for Exclusion:

- The subject has PAD Fontaine Stage III or IV (pain at rest, nonhealing ulceration, or gangrene).
- The subject has evidence of nonatherosclerotic PAD.
- The subject has >25% variability in ACD based on treadmill testing during the screening period.
- The subject has lower extremity arterial reconstruction (surgical or endovascular) or sympathectomy within 3 months before Screening.
- The subject is eligible for surgical/interventional reconstruction.
- The subject had a myocardial infarction or major cardiac surgery within 3 months before Screening.
- The subject has congestive heart failure (New York Heart Association Class III/IV).
- The subject has uncontrolled diabetes mellitus (glycosylated hemoglobin [HbA1c] >9%) or diabetic polyneuropathy).

- The subject has any other illness that significantly limits exercise capacity or other medical condition that limits participation (in the judgement of the investigator).
- The subject has received any prohibited medication (Section 7.3) within 14 days before Randomization (Day 1)
- The subject is undergoing the supervised exercise training program by the time of Screening and is going to continue this program due to its effectiveness.

Criteria for Evaluation and Analyses:

The primary endpoint is the percent change in ICD from Baseline to 12 weeks. The secondary endpoints are:

- The percent change in ICD from Baseline to 2 and 24 weeks.
- The change in ACD from Baseline to 2, 12, and 24 weeks.
- Proportion of patients having rest pain at 12 and 24 weeks.
- Proportion of patients having revascularization procedures at 24 weeks.
- Change in 36-item Short Form Survey (SF-36) at 12 and 24 weeks.

Statistical Considerations:

The primary and secondary endpoints will be analyzed in randomized patients who received at least 1 dose of study drug.

Percent change from Baseline in ICD and change from Baseline in SF-36 will be analyzed using a mixed model for repeated measurements (MMRM) analysis of covariance with treatment, center, sex, age group, visit, treatment-by-visit interaction as fixed effects, Baseline as covariate, and subject as a random effect. Comparisons between actovegin and placebo will be performed on all assessment points. Based on a missing at random assumption, this analysis will be performed using observed case data only. The effect at each time point for each treatment is allowed to vary freely and an unstructured covariance matrix is assumed.

Proportion of subjects having rest pain and proportion of patients having revascularization procedures will be analyzed at all time points by logistic regression adjusting for treatment.

Sample Size Justification: Assuming a standard deviation of 85% for the percent change from Baseline in ICD and a 20% drop-out rate, a total of 366 subjects (183 per treatment group) is sufficient to achieve at least 80% power to detect a 28% difference in percent change from Baseline in ICD between actovegin and placebo by a 2-sample t-test with a 0.05 two-sided significance level.

The sample size justification is based on published data for the ICD for naftidrofuryl, for which the difference in percent change from Baseline in ICD between naftidrofuryl and placebo is approximately 28%, while the corresponding pooled standard deviation is approximately 85%.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical study supplier list. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator(s) from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

ABI	ankle brachial index
ACD	absolute claudication distance
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CPMP	Committee for Proprietary Medicinal Products
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HbA1c	glycosylated hemoglobin
hCG	human chorionic gonadotropin
IC	intermittent claudication
ICD	initial claudication distance
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IP	investigational product
IRT	interactive response technology
IV	intravenous
LFT	liver function tests
LSU	lipasemic unit
MedDRA	Medical Dictionary for Regulatory Activities
Med ID	medication identification number
MMRM	mixed model for repeated measures
PAD	peripheral arterial disease
PSUR	Periodic Safety Update Report
PTE	pretreatment event
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	36-item Short Form Survey
SUSAR	suspected unexpected serious adverse reaction
TID	3 times daily
ULN	upper limit of normal

3.4 Corporate Identification

Takeda	TDC Japan, TDC Asia, TDC Europe, and/or TDC Americas, as applicable
TDC-Americas	Takeda Development Center Americas, Inc.

4.0 INTRODUCTION

4.1 Background

Peripheral arterial disease (PAD), also known as peripheral arterial occlusive disease is a manifestation of systemic atherosclerosis defined by progressive stenosis or occlusion within the arteries of the lower extremities [1]. PAD affects approximately 202 million adults worldwide [2]. The prevalence of PAD increases with age and the number of vascular risk factors (eg, diabetes, smoking, hypertension, hypercholesterolemia, age, sex, family history) [1,3].

More importantly, it is a marker of atherosclerotic disease burden, and is associated with increased mortality from cardiovascular and cerebrovascular causes [1,3].

The decreased blood flow to the legs caused by PAD may be mild or severe, resulting in a broad range of symptoms. Patients may not suffer recognizable limb symptoms, or they may experience intermittent claudication (IC), or manifest symptoms of severe limb ischemia. IC, the most common symptom of PAD, is defined as fatigue, cramping, or overt pain of the gluteal, thigh, or calf muscles, that is consistently provoked by exercise and that is reproducibly relieved by rest.

Patients with IC are often limited in their daily activities owing to their walking impairment and in turn experience a diminished quality of life. With continued exposure to atherosclerotic risk factors, PAD may progress to critical limb ischemia, which portends a severe diminution in quality of life, and is associated with a high rate of amputation and a marked increase in short term mortality. Thus, PAD is a common manifestation of atherosclerosis that is associated with a range of symptoms, a variable impact on quality of life, and a heightened risk of cardiovascular ischemic events [1].

Actovegin is a deproteinized hemoderivate from calf blood that has been made free of pyrogens and antigens through a stepwise ultrafiltration production process.

Actovegin contains physiological blood components, including vitamins, amino acids, lipids, oligosaccharides and oligopeptides, nucleosides, intermediate products of carbohydrate and fatty acid metabolism, as well as constituents of cellular membranes, such as glycosphingolipids. It has pleiotropic metabolic, neuroprotective, and regenerative properties [4]. Experimental studies have shown that actovegin improves oxygen utilization and uptake, as well as energy metabolism and glucose uptake [5-7]. Actovegin has been shown to possess neuroprotective effects and to increase neuronal survival under ischemic conditions [8]. It also reduces amyloid beta-induced apoptosis along with decreasing reactive oxygen species formation [9], modulates nuclear factor kappa B activity[10], and inhibits the nuclear enzyme poly(adenosine diphosphate ribose) polymerase, which can also partially explain its neuroprotective properties [11]. Actovegin exerts positive effects on microcirculation and microvascular endothelium, increasing capillary blood flow rate and reducing pericapillary zone and arteriolovenular shunting of blood flow [12].

Clinical efficacy data for actovegin provide evidence for the treatment of disturbances of the cerebral circulation including dementia [13,14] and post stroke cognitive impairment [14]. Several randomized controlled trials and many uncontrolled studies have been conducted for these indications. Available clinical data also support the use of actovegin for the treatment of diabetic

polyneuropathy [15]. The efficacy of actovegin for these indications is further supported by nonclinical pharmacodynamic research. The efficacy data are also supportive for peripheral perfusion disorders with positive study outcomes for maximal and pain-free walking distance in PAD and healing time in venous ulcer disease [16-20].

Actovegin received its first marketing authorization in the Federal Republic of Germany in 1976 and remains on the market in more than 20 countries (eg, in several countries in the Commonwealth of Independent States and in a few countries in Europe and Asia region). It exists in different formulations for oral, intravenous (IV), and intramuscular usage. Actovegin has been approved for the following indications (which vary among countries):

- Symptomatic treatment of cognitive impairment including post-stroke cognitive impairment and dementia.
- Symptomatic treatment of peripheral perfusion disorders and their sequelae.
- Symptomatic treatment of diabetic polyneuropathy.

Actovegin has been used clinically for over 40 years. Due to its composition of biological constituents present under normal physiological conditions and stringent production process, the drug has an excellent safety profile, reflected by clinical experience equivalent to an exposure to the drug of more than 1,200,000 patient years (Periodic Safety Update Report [PSUR] 2014 submitted to the Austrian Agency for Health and Food Safety). The profile of adverse drug reactions (ADRs) has been consistent across PSURs without particular target organ toxicity.

4.2 Rationale for the Proposed Study

Actovegin has been used since the 1970s for the treatment of PAD of varying degrees of severity. Several trials have evaluated the efficacy of actovegin (IV) in patients with mainly Fontaine Stage II and III PAD.

A randomized, open-label, 8-week study has been conducted to investigate the effect of actovegin on ischemic syndrome of the lower extremities in patients with type 1 and type 2 diabetes, in comparison with sulodexide [16]. Patients were randomized to receive either IV infusions of actovegin (2000 mg once daily; n=12) or sulodexide (1200 lipasemic units [LSU] per day; n=14) for 2 weeks followed by oral administration of the 2 drugs for a further 6 weeks (1200 mg/day and 1000 LSU per day respectively). Both treatments increased maximum pain-free walking time after 8 weeks of treatment ($p<0.05$). However, actovegin treatment significantly increased maximum pain-free walking time after 2 weeks of treatment versus Baseline ($p<0.05$), whereas treatment with sulodexide did not. Additionally, the relative increment in pain-free walking time was greater in the actovegin group compared with the sulodexide group (95.1% versus 38.1% respectively; $p<0.05$).

A randomized, double-blind, placebo-controlled, parallel-group study including 60 patients with Stage II PAD was conducted [17]. All patients took part in a regular physical training program for 12 weeks, at least 4 weeks before randomization. Patients then received daily IV infusions of actovegin 20% (250 mL/day) or placebo (saline 250 mL/day) for a period of 4 weeks. The primary

endpoint, pain-free walking on a treadmill, increased by 27% (from 73 to 93 meters) in the actovegin group and decreased in the placebo group by 12% (10 meters). The difference between the 2 groups was statistically significant ($p<0.001$). A similar result was obtained with maximum walking distances (+25% versus -10.4% for actovegin and placebo, respectively; $p<0.01$).

Horsch et al. conducted a randomized, double-blind, placebo-controlled study including 138 patients with Stage II PAD [18]. Actovegin 20% (250 mL) and matching placebo were administered as daily IV infusions over a 3-week period. Efficacy was evaluated by means of a responder analysis where response was defined as a 35% increase from Baseline in pain-free walking distance measured on a treadmill. There were 57% responders in the actovegin group compared with 33% in the placebo group ($p=0.01$).

In another double-blind study, Müller-Bühl et al. evaluated the efficacy and compatibility of actovegin 20% infusion (250 mL) versus placebo (0.9% saline 250 mL) in patients with Stage II PAD [19]. In this study, actovegin and placebo were administered intra-arterially into the femoral artery of the walking distance-limiting leg; patients were required to have a steady state in walking distance before they were randomized to receive either actovegin (n=40) or placebo (n=40).

Infusions were administered daily, except for weekends, for a period of 4 weeks and training was ceased with the commencement of the treatment phase. Actovegin therapy resulted in an increase of pain-free walking distance from 112 to 162 meters (49%) and maximum walking distance from 171 to 266 meters (59%). In the placebo group, pain-free walking distance increased from 114 to 135 meters (23%), and maximum walking distance from 176 to 201 meters (17%). The differences between the 2 groups were significant for both parameters ($p<0.05$). Following the discontinuation of actovegin treatment and placebo, an 8-week follow-up showed that the walking distance fell markedly in the placebo group, compared with patients previously treated with actovegin.

A randomized, single-blind study has also been performed to compare the efficacy of actovegin and bencyclane in Stage III PAD [20]. Fifty-eight patients were randomized to receive either actovegin 20% infusion (20 intra-arterial infusions) or 250 mg bencyclane in 250 mL saline 0.9% over a period of 4 weeks. Endpoint analyses revealed that after 4 weeks, 23.1% of patients treated with actovegin experienced pain at night compared with 61.5% of patients treated with bencyclane ($p<0.05$). No patients treated with actovegin reported permanent pain after 4 weeks, whereas 16% of patients treated with bencyclane did ($p<0.05$). Analgesic use at 4 weeks was also lower in patients treated with actovegin compared with those treated with bencyclane (28.7% versus 42.3% respectively; $p<0.05$). Finally, both treatments increased pain-free walking distances (29.2±14.6 meters and 25.8±18.7 meters for the actovegin and bencyclane groups respectively) but there was no statistically significant difference between the 2 groups.

In summary, IV treatment with actovegin has been shown to increase initial walking distance and relieve pain symptoms in patients with PAD in small, double-blind, controlled trials. To date, no large-scale randomized placebo-controlled trials have been undertaken to support this observation. This will be the first large-scale study to provide data in support of the use of actovegin (IV and oral) in the treatment of patients with PAD.

4.3 Benefit/Risk Profile

This current study investigates the efficacy and safety of actovegin compared to placebo in subjects with PAD. Several small randomized, controlled, clinical studies have evaluated the efficacy of actovegin in patients with PAD, mainly in Fontaine Stages II (mild (a), moderate, severe (b) claudication) and III (ischemic pain at rest). Although some actovegin studies were performed before implementation of current clinical investigation guidelines, such as the European Committee for Proprietary Medicinal Products (CPMP)/ EWP/714/98 "Note for guidance on clinical investigation of medicinal products for treatment of peripheral arterial occlusive disease," most studies used the primary endpoints recommended in the European guidelines (eg, walking distance for PAD Stage II).

As summarized in Section 4.2 results of these randomized, controlled trials showed short-term benefit in initial walking distance and pain symptoms with actovegin solution for infusion in populations with PAD.

The safety and tolerability of actovegin in clinical trials was broadly similar to that observed following placebo administration.

The following undesirable effects are reflected in the Company Core Data Sheet for actovegin (2016) in accordance with the classification of the frequency of an ADR based on the Council for International Organizations of Medical Sciences guidelines:

- Immune system disorders: allergic reactions (hypersensitivity, drug fever, shock symptoms).
- Skin and subcutaneous tissue disorders: urticaria, flush.

The frequency of these ADRs has been classified as rare (≥1/10,000 to <1/1,000).

The safety profile for actovegin suggests that it is well tolerated in all approved indications and the known risks can be mitigated by the appropriate use of the product, as directed by the label. This includes the monitoring for hypersensitivity reactions and adherence to sterile practices on handling and administrating the intravenous product.

Overall, a favorable benefit-risk profile has been established to support the clinical use of actovegin.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to investigate the efficacy of actovegin for the symptomatic treatment of PAD Fontaine Stage IIB.

5.1.2 Secondary Objectives

- To investigate the effect of actovegin in sustained improvement in claudication distance of subjects with PAD Fontaine Stage IIB.
- To investigate the effect of actovegin on patients' quality of life.

5.1.3 Safety Objective

- To evaluate the safety of actovegin compared with placebo.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is the percent change in initial claudication distance (ICD) from Baseline to 12 weeks of study treatment.

5.2.2 Secondary Endpoints

- The percent change in ICD from Baseline to 2 and 24 weeks after randomization.
- The change in absolute claudication distance (ACD) from Baseline to 2, 12, and 24 weeks after randomization.
- Proportion of patients having rest pain at 12 and 24 weeks after randomization.
- Proportion of patients having revascularization procedures at 24 weeks after randomization.
- Change in 36-item Short Form Survey (SF-36) at 12 and 24 weeks after randomization.

5.2.3 Additional Endpoints: Safety

- Safety and tolerability of actovegin will be evaluated by assessment of adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiogram (ECG), and physical examination.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a randomized, multi-center, parallel group, double-blind, placebo-controlled phase 3b study to evaluate the efficacy and safety of actovegin 12-week treatment given intravenously and subsequently orally in subjects with PAD Fontaine Stage IIB.

A total of 366 subjects with PAD Fontaine Stage IIB will be enrolled in approximately 17 to 25 sites in 3 countries (Russia, Kazakhstan, and Georgia).

The study will consist of a 1- to 2-week Screening Period, Randomization, 12-week Treatment Period, and 12-week Follow-up Period. The overall study duration will be 25 to 26 weeks.

Subjects will enter a 1- to 2-week Screening Period during which, the stability of the subject's condition will be verified, a diagnosis of PAD will be confirmed, and subjects with high variability in the claudication distance will be detected and excluded. For this purpose, 2 treadmill tests will be performed within a time interval of ≥1 week (ie, 7 days). Subjects having a change of more than 25% in the ACD during the Screening Period will be excluded.

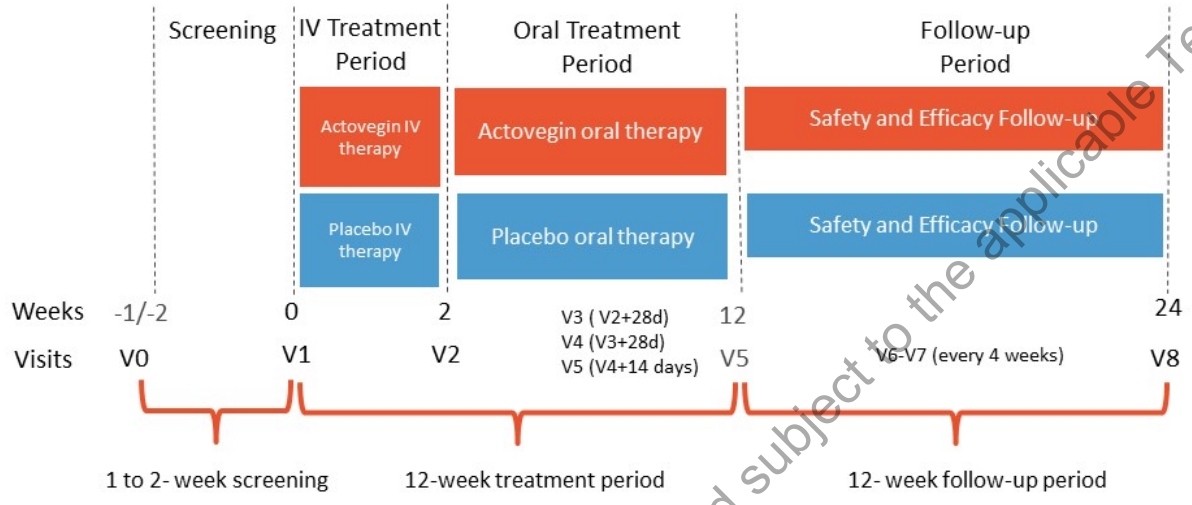
Subjects with a history of stable intermittent claudication with symptoms that have been present continuously for at least 6 months at the time of Screening. A diagnosis of PAD (ICD of <200 meters) will be confirmed by ultrasound color duplex imaging and treadmill test.

Eligible subjects will be randomized to receive either actovegin or placebo in a 1:1 ratio. The treatment period will include 2 weeks of IV infusions of actovegin (deproteinized hemoderivate) at a dose of 1200 mg/day, followed by 10 weeks of oral treatment in tablets at a dose of 1200 mg/day (two 200 mg tablets 3 times daily [TID]). Matched placebo (placebo ampoules and placebo tablets) will be used throughout the treatment period to maintain blinding. The overall treatment duration will be 12 weeks.

A 12-week follow-up period with no investigational medicinal product (IMP) treatment will follow the 12-week treatment period to examine sustained efficacy after treatment as well as safety once actovegin treatment has stopped.

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



V=visit.

6.2 Justification for Study Design, Dose, and Endpoints

The randomized parallel group, double-blind, placebo-controlled study design is consistent with the recommendations in CPMP/EWP/714/98 "Note for guidance on clinical investigation of medicinal products for treatment of peripheral arterial occlusive disease."

The dosing regimen for this study reflects the labelling except that the oral treatment will be for a longer period than stipulated in the label. The recommended dose for actovegin is 800 to 2000 mg (20-50 mL) intravenously for 4 weeks. The recommended dose for the tablet formulation is 1 to 2 tablets (each tablet containing 200 mg actovegin) TID with an average treatment duration of 4 to 6 weeks. The oral dosing regimen in the current study is 2 tablets (200 mg) TID (1200 mg/day) for 10 weeks.

The efficacy of actovegin 1000 mg IV was demonstrated in a comparative randomized study in patients with PAD Fontaine Stage IIB. Maximum walking distance increased after 4 weeks of treatment by 100.7% in the actovegin group compared with 67% and 8.1% in the naftidrofuryl and vitamin B groups, respectively [21]. In another open-label controlled study, actovegin was administered at 1000 mg IV daily for 10 days and showed an increase of pain-free walking distance comparable with pentoxifylline group. Analyses of microcirculation in the skin using laser Doppler flowmetry showed that actovegin had a number of significant effects better pronounced when compared with pentoxifylline group [22].

This prolonged oral treatment period has demonstrated safety and efficacy in previous actovegin trials.

The primary endpoint of change from Baseline in ICD was chosen as intermittent claudication as it is a key symptom of Stage II PAD and is recommended in the European Medicines Agency (EMA) guideline "Note for guidance on clinical investigation of medicinal products for treatment of peripheral arterial occlusive disease."

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the actovegin, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an ethics committee or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before randomization or first dose.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before entry into the study:

1. The subject is male or female and aged 40 to 75 years, inclusive.
2. The subject has a confirmed history of stable intermittent claudication with symptoms that /have been present continuously for at least 6 months at the time of Screening.
3. The subject has a diagnosis of PAD (Code I70.2 according to the international classification of diseases-10th revision) Fontaine Stage IIB confirmed by ultrasound color duplex imaging.
4. The subject has a history of stable smoking habits for at least 3 months before Randomization (Day 1).
5. The subject has a resting Doppler ankle-brachial index of ≤0.9.
6. The subject has intermittent claudication with ICD <200 meters.
7. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
8. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization before the initiation of any study procedures.
9. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use barrier method of contraception (eg, condom with or without spermicide) from signing of informed consent throughout the duration of the study or for 30 days after the last dose in case of premature termination. The female partner of a male subject should also be advised to use a highly effective/effective method of contraception throughout the duration of the study or for 30 days after the last dose in case of premature termination.
10. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use an effective or a highly effective method of contraception from signing of informed consent throughout the duration of the study or for 30 days after the last dose in case of premature termination. Definitions of effective/highly effective methods of contraception are defined in Section 9.1.12 and reporting responsibilities are defined in Section 9.1.13.
11. The subject has a history of stable PAD therapy for at least 2 weeks before Screening and is not newly diagnosed with PAD.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria after the screening period will not qualify for entry into the study:

1. The subject has PAD Fontaine Stage III or IV (pain at rest, non-healing ulceration, or gangrene).
2. The subject has evidence of nonatherosclerotic PAD.
3. The subject has >25% variability in ACD based on treadmill testing during the screening period.
4. The subject has lower extremity arterial reconstruction (surgical or endovascular) or sympathectomy within 3 months before Screening.
5. The subject is eligible for surgical/interventional reconstruction.
6. The subject had a myocardial infarction or major cardiac surgery within 3 months before Screening.
7. The subject has congestive heart failure (New York Heart Association Class III/IV).
8. The subject has uncontrolled diabetes mellitus (glycosylated hemoglobin [HbA1c >9%]) or diabetic polyneuropathy.
9. The subject has any other illness that significantly limits exercise capacity or other medical condition, including any psychiatric disorder that limits participation (in the judgement of the investigator).
10. The subject has received any prohibited medication (Section 7.3) within 14 days before Randomization (Day 1).
11. The subject has received any investigational compound within 30 days before Screening.
12. The subject has received actovegin as a therapeutic agent within 30 days prior Screening.
13. The subject is an immediate family member, study site employee, in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling), or may consent under duress.
14. The subject has, in the judgment of the investigator, clinically significant abnormal hematological parameters of hemoglobin, hematocrit, or erythrocytes at Screening.
15. The subject has a history of hypersensitivity or allergies to actovegin or similar preparations or the excipients.
16. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 6 months before Screening.
17. If female, the subject is pregnant or lactating or intending to become pregnant before participating in this study and during the study, or intending to donate ova during such time period.

18. The subject has participated in another clinical study within 30 days before Screening.
19. The subject is undergoing the supervised exercise training program by the time of Screening and is going to continue this program due to its effectiveness.

7.3 Excluded Medications and Treatments

Concomitant and prior medication should be checked carefully and documented in the electronic case report form (eCRF).

Medications that are prohibited during the course of the study are listed as follows:

Alprostadil and other prostaglandins	Angiogenic growth factors
Chronic use of nonsteroidal anti-inflammatory agents	Cilostazol
Ginkgo bilobae foliorum extract	L-carnitine
L-lysine aescinat	Naftidrofuryl
Nicotinic acid	Pentoxifylline
Sulodexide	Vincamine
Solcoseryl (nontopical forms)	L-arginine based compounds

A supervised exercise training program, hyperbaric oxygenation and any type of physiotherapy that can potentially influence peripheral circulation will not be allowed during the study.

Concomitant medication for any other acute or chronic medical condition can be started or continued according to prescription by a healthcare professional. Subjects should be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator. Additional information on concomitant PAD therapy is provided in Section 8.1.1.2.

7.4 Diet, Fluid, Activity Control, Treatment Facilities, and General Recommendations and Restrictions

It is expected that advice on lifestyle changes to minimize vascular risk factors (eg, smoking cessation and regular physical exercise) has been given to all subjects before entering the study.

It is expected that the supervised exercise training program is tried for subjects before they are considered for entering the trial unless otherwise justified (supervised exercise training program was performed with no effect, or was recommended, but was not done due to subject related reasons). Proper documentation is required.

Smoking habits should be stable for at least 3 months at the time of Randomization (Day 1) and throughout the study. Smoking status and comedications will be assessed and documented. These therapies should be maintained at a stable level throughout the study.

In addition, the treatment and status of glycemic control in diabetic patients and the occasional use of nonsteroidal anti-inflammatory agents may also affect PAD. These medications should be reviewed and documented in the eCRF.

During the IV Treatment Period, either hospitalization or day hospital is required to provide this treatment procedure.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the eCRF using the following categories listed below. For screen failure subjects, refer to Section 9.1.15.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

   - Liver Function Test (LFT) Abnormalities

     Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.10), if the following circumstances occur at any time during study drug treatment:

     – alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × the upper limit of normal (ULN), or
     – ALT or AST >5 × ULN and persists for more than 2 weeks, or
     – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN, or
     – ALT or AST >3 × ULN with appearance of at least 1 of the next symptoms: fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

2. Significant protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category).

5. Study termination. The sponsor, ethics committee, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.13.
7. Disease progression. There are clinical signs of critical limb ischemia (pain at rest, ulcer formation, and gangrene) supported by instrumental methods which require revascularization procedure.
8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit at the earliest possible date. The Early Termination Visit for subjects who discontinue the study before completing the Oral Treatment Period will be identical to Visit 5. The Early Termination Visit for subjects who discontinue the study after completing the Oral Treatment Period will be identical to the Final Follow-up visit. The Follow-up Period is not required for subjects who discontinue the study early. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to actovegin (400 mg/10 mL and 200 mg) active and matching placebo as described below. Study medication will be packed in a blinded fashion.

8.1.1.1 Investigational drug

Actovegin ampoules (400 mg/10 mL) and tablets (200 mg)

The study drug (actovegin) will be supplied as ampoules (400 mg/10 mL) and tablets (200 mg). Actovegin (deproteinized hemoderivate) is commercially available both as ampoules and tablets. The commercially available actovegin ampoules and tablets will be packed and labeled in a blinded fashion by the contract manufacturing organization (CCI [redacted] and therefore both products are considered investigational medicinal product.

Takeda GmbH, Austria is the original manufacturer of the 400 mg/10 mL actovegin ampoules. One ampoule contains actovegin 400 mg in 10 mL water for injection. The solution is clear, yellowish, and almost free from particles. The color can change to a stronger yellow color over the course of the shelf life. Taking into account the color of the actovegin solution and the different design of the ampoules, an unblinded pharmacist will be included in the site study team and will be responsible for preparation of the investigational product (IP) during the IV treatment period.

The ampoules will be packed into 7-day (21 ampoules for 1 week plus 3 ampoules for 1 day) In-Patient kits. Dosing consists of 3 ampoules daily.

Each ampoule will bear a multilingual booklet label or a single language label, including pertinent study information. Each kit of 400 mg/10 mL actovegin will bear a multilingual booklet label or a single language label that includes pertinent study information along with caution statement.

Takeda GmbH, Germany is the primary manufacturer of the 200 mg actovegin tablets. The tablets are round, biconvex, bright greenish-yellow, film-coated, shiny, and bear no print.

The tablets will be packed into child-resistant bottles, containing a total of 50 tablets each. Dosing consists of 6 tablets daily.

Each bottle of 200 mg actovegin will bear a multilingual booklet label or a single language label that includes pertinent study information along with caution statement. Each bottle kit will also bear a multilingual booklet label or a single language label that includes pertinent study information along with caution statement.

Labels will be in the appropriate language where the study medication is dispensed.

Placebo ampoules and tablets

The placebo ampoules to match 400 mg actovegin ampoules will be commercially available ampoules containing 10 mL 0.9% NaCl solution for infusion.

CCI is the original manufacturer of the placebo ampoules. The ampoules will be sourced, packed, and labeled at CCI.

The placebo ampoules will be packed into 7-day (21 ampoules for 1 week plus 3 ampoules for 1 day) In-Patient kits. Dosing consists of 3 ampoules daily.

Each ampoule will bear a multilingual booklet label or a single language label, including pertinent study information. Each kit of placebo ampoules will bear a multilingual booklet label or a single language label that includes pertinent study information along with caution statement.

The placebo tablets to match 200 mg actovegin tablets will be manufactured by CCI and then packed and labeled at CCI.

The tablets will be packed into child-resistant bottles, containing a total of 50 tablets each. Dosing consists of 6 tablets daily.

Each bottle of placebo tablets will bear a multilingual booklet label or a single language label that includes pertinent study information along with caution statement. Each bottle kit will also bear a multilingual booklet label or a single language label that includes pertinent study information along with caution statement.

Labels will be in the appropriate language where the study medication is dispensed.

8.1.1.2 Companion Medication

Concomitant PAD Therapy

Subjects should continue their current treatment for PAD and for prevention of cardiovascular events. These therapies should be optimized and stable for at least 2 weeks before Screening and throughout the study.

Therapy for the treatment of PAD and for prevention of cardiovascular events includes:

- Antiplatelet drugs and anticoagulants (except medications listed in Section 7.3).
- Lipid-lowering agents.
- Antihypertensive drugs.

In addition to the listed medications for PAD, the treatment and status of glycemic control in diabetic patients and the occasional use of nonsteroidal anti-inflammatory agents may also affect PAD. These medications should be reviewed and documented in the eCRF.

8.1.1.3 Ancillary Materials

The sponsor will further supply the sites with bags of 250 mL 0.9% NaCl solution for infusion, opaque infusion sets, cover bags for the infusion bags, and ancillary labels to affix to the cover bags at the sites.

CCI is the original manufacturer of 0.9% NaCl solution for infusion bags, 250 mL.

8.1.1.4 Sponsor-Supplied Drug

Actovegin ampoules (400 mg/10 mL), tablets (200 mg), placebo ampoules, and placebo tablets will be supplied by the sponsor. In addition, infusion bags containing 250 mL 0.9% NaCl solution for infusion will be supplied by the sponsor. Opaque infusion sets, cover bags and ancillary labels for the infusion bags will be supplied by the sponsor.

8.1.2 Storage

Study drug ie, actovegin ampoules (400 mg/10 mL), actovegin tablets (200 mg), placebo ampoules, placebo tablets, and ancillary materials ie, 0.9% NaCl solution for infusion bags, opaque infusion sets, cover bags, and ancillary labels must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug, and ancillary materials must be stored under the conditions specified on the label (below 25ºC [77ºF]; do not freeze), protected from light and remain in the original container until dispensed. Please consult the Pharmacy Manual for further information. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

8.1.3.1 IV Treatment Period (Week 0 to 2)

Each subject who satisfies the eligibility criteria will be randomly assigned to receive either actovegin or placebo via interactive web response system.

After Randomization (Visit 1, Day 1), subjects will receive 3 ampoules of either actovegin 400 mg/10 mL or placebo/10 mL in 250 mL 0.9% NaCl (total infusion volume will be 280 mL) as a single infusion. The infusion rate will be about 2 mL per minute (40 to 50 drops/minute). Total infusion duration should not be less than 112 minutes. Subjects will receive 1 infusion per day for 14 days. Starting on Day 2, the start time of infusion should be the same as the start time of infusion on Day 1 ±2 hours. The investigator or designee must ensure that the sponsor-supplied drug is prepared and administered according to the Pharmacy Manual.

IP infusions must be performed at the investigational site under medical supervision. During the first 15 minutes of the first infusion, the supervision should be carried out by the investigator (or designated physician) in order to detect possible allergic reactions and ensure urgent measures to prevent or treat them.

8.1.3.2 Oral Treatment Period (Week 3 to 12)

When the IV Treatment Period is over (Visit 2), subjects will be dispensed a box with 4 bottles containing a total 200 tablets of actovegin 200 mg or placebo. Subjects will be instructed to take 2 tablets of actovegin 200 mg or placebo TID, in total 6 tablets per day starting the day after the end of the IV treatment period. Subjects will receive study drug for 4 weeks of treatment and the subject will be reminded to bring the study medication bottle (including any unused study medication) to the following study visit.

A further box with 4 bottles containing a total of 200 tablets of actovegin 200 mg or placebo will be dispensed to the subjects at the third visit (Visit 3) so that the subjects will receive study drug for another 4 weeks of treatment. Subjects will be instructed to take 2 tablets of actovegin 200 mg or placebo TID, in total 6 tablets per day. The subject will also be reminded to bring the study medication bottle (including any unused study medication) to the following study visit.

At the fourth visit (Visit 4), subjects will be dispensed a last box containing 2 bottles containing a total of 100 tablets of actovegin 200 mg or placebo, so that they receive study drug for 2 weeks treatment. Subjects will be instructed to take 2 tablets of actovegin 200 mg or placebo TID, in total 6 tablets per day. The subject will also be reminded to bring the study medication bottle (including any unused study medication) to the following study visit (Visit 5).

Thereafter, subjects will move into the follow-up phase where they will not receive any further study drug.

Table 8.a describes the dose and ampoule/tablet count that will be provided to each group.

Table 8.a Dose and Regimen

Treatment Group	Treatment Phase	Treatment Description	Treatment Dose
A	IV Treatment	Actovegin 400 mg/10 mL	3 ampoules in 0.9% NaCl 250 mL (1200 mg/280 mL IV infusion) per day
B	IV Treatment	Placebo/10 mL	3 ampoules in 0.9% NaCl 250 mL (280 mL IV infusion) per day
A	Oral treatment	Actovegin 200 mg/tablet	6 tablets per day from bottle
B	Oral treatment	Placebo/tablet	6 tablets per day from bottle

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an overdose page of the eCRF, in order to capture this important safety information consistently in the database.

Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

There has been no experience of overdose with actovegin. According to nonclinical study data, actovegin does not show toxic effects with doses of up to 30 to 40 times higher than the dose recommended for human use.

No compound-specific instructions of overdose treatment exist. On the basis of its pharmacology, no undesirable effects would be anticipated.

8.2 Study Drug Assignment and Dispensing Procedures

The investigator or the investigator's designee will access the interactive response technology (IRT) system at Screening to obtain the study-specific subject identification number (subject number).

The investigator or the investigator's designee will use the IRT system to randomize the subject into the study. During this contact, the investigator or the investigator's designee will provide the necessary subject-identifying information, including the subject number assigned at Screening.

At drug-dispensing visits, the investigator or the investigator's designee will again contact the IRT system to register the visits. At Visits 1, 2, 3, and 4 for all subjects in both treatment groups, a medication identification number (Med ID) will be assigned by the IRT system and provided to the unblinded site pharmacist/nurse via email notification.

If sponsor-supplied drug is lost or damaged, the unblinded site pharmacist/nurse can request a replacement from the IRT system.

8.3 Randomization Code Creation and Storage

Takeda randomization personnel or designee will generate the randomization schedule for the study; an IRT system will be used in a centralized fashion for subject randomization and study medication assignments.

All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The study medication blind will be maintained using the IRT system. The principal investigator at each study site will receive instructions on obtaining the medication assignment through the IRT system.

Investigators, clinical site team staff involved in subject care or clinical examinations, statistical team, data-management team, sponsor and CRO study teams, and subjects will be blinded regarding the type of therapy until the database lock, except an unblinded study monitor from the sponsor or a designee. Staff at the pharmacy (study nurse, pharmacist) will not be blinded. All bags and infusion system for infusions will be closed and sealed material does not allow the unauthorized opening, in order to maintain blinding.

The site-designated study personnel will maintain the investigational drug blind information. During regularly scheduled monitoring visits, an unblinded study monitor from the sponsor or a designee will perform an inventory of investigational drug unassigned and assigned treatment box/bottles. All assigned and unassigned treatment packages will be reconciled and returned to the sponsor or a designee before study closure.

8.5 Unblinding Procedure

The study medication blind shall not be broken by the investigator unless information concerning the study medication is necessary for the medical treatment of the subject. If possible, the sponsor/designee should be notified before the study medication blind is broken.

For unblinding a subject, the study medication blind can be obtained by accessing the IRT system. In case of IRT system unavailability, the investigator should follow the instructions for the backup unblinding system (provided as a separate document). The sponsor/designee must be notified immediately if the study medication blind is broken. The date, time, and reason the blind was broken must be recorded in the source documents and on the appropriate eCRF.

If any site personnel become unblinded, study medication must be stopped immediately and the subject must be withdrawn from the study. The reason for withdrawal should be recorded as "Significant Protocol Deviation."

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug (actovegin ampoules/placebo, actovegin tablets/placebo) and ancillary material (0.9% NaCl solution for infusion, opaque infusion sets, cover bags, and ancillary labels) is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and sending by e-mail/fax per instructions provided on the form/by recording in the IRT system. If there are any discrepancies between the packing list versus the actual product received, Takeda or designee must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates (monitored via the IRT system).
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the Medication ID/other used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- Unblinded site representative or unblinded monitor will review the randomization schedule and subject dosing log to ensure all subjects received the correct dose of study drug.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IRT system will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date and amount dispensed including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject (by subject identifier) to whom sponsor-supplied drug is dispensed.

The investigator or its designated site staff administering the study medication (actovegin/placebo infusion) must complete an individual subject accountability log to document if infusion was complete or if incomplete and study medication was returned to the pharmacy, including the date and amount returned to the pharmacy, including initials, seal, or signature of the person administering the infusion.

All study drug not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained before the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, and race as described by the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at, or before, signing of informed consent, including psychiatric history (any psychiatric disorders is exclusion criteria). Ongoing conditions are considered concurrent medical conditions (Section 9.1.9).

Medication history information to be obtained includes any medication relevant to eligibility criteria (Sections 7.1, 7.2, 7.3) stopped at 14 days before Randomization (Day 1).

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment before the first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment before the first dose examination.

9.1.4 Weight and Height

Weight and height of subjects should be measured while wearing indoor clothing and no shoes. Values are to be reported to 1 decimal place. Height will be measured at V1. Weight will be measured at V1, V5, and V8.

9.1.5 Smoking Status and Physical Activity

Smoking status will be classified as follows:

1. Never smoked.
2. Current smoker (information about years of smoking and current number of cigarettes per day will be collected).
3. Former smoker (information about years of smoking, approximate number of cigarettes smoked per day previously, and date of cessation will be collected).

For the purposes of the study, e-cigarette use should not be considered in determination of smoking history. One gram of tobacco = 1 cigarette.

Smoking status will be checked every study visit.

Physical activity will be evaluated using the Physical Activity Questionnaire developed by FSI "National Medical Research Center for Preventative Medicine" of the Ministry of Healthcare of the Russian Federation as part of national clinical guidelines "Medical assistance for optimizing physical activity in adults."

Patients should be provided with the Physical Activity Questionnaire in a language in which they are fluent. The questionnaire contains 8 statements describing current level of patient's physical activity, each statement is assigned to score from 1 (the lowest activity) to 8 (the highest activity). Patients should complete the Physical Activity Questionnaire by circling the statement that best describes their current physical activity. The investigator must check that the questionnaire is completed appropriately.

Physical activity level will be checked at every study visit.

9.1.6 Vital Sign Procedure

Vital signs will include blood pressure (systolic and diastolic) and pulse (beats/minute) after resting not less than 5 minutes in a sitting position. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hours before or after the scheduled blood draw.

9.1.7 Efficacy Measurements

9.1.7.1 Treadmill testing

A treadmill is a device used for walking or running while staying in place. In this study, this method will be used to define claudication distances. Claudication distance will be measured by using the constant workload protocol (constant speed 3.0 km/h and 10% grade on treadmill).

From signing of the informed consent during the screening period through the Randomization visit, the treadmill test will be conducted twice. The first test is to be performed during the Screening period. The screening period length should be a maximum of 2 weeks. The second treadmill test should be repeated within a time interval of ≥ 1 week (ie, 7 days) from the first

treadmill test. It is acceptable for the second treadmill test to be completed on the day of Randomization (Day 1).

Subjects with high variability in ACD [>25% for the maximum claudication distance] will be excluded.

Variability of ACD will be calculated by the investigator using the formula:

ACD % of variation = [ACD Test 2 − ACD Test 1] / Test 1 × 100%

If a subject is randomized for the study therapy, the Day 1 testing will be used as Baseline.

The following steps should be followed for the treadmill test:

- The test should be performed on a treadmill with changeable incline and speed.
- The subject should take off their shoes and outerwear.
- The subject should not have a meal within 3 hours before the test, and should avoid physical exercises and stress within 12 hours before the test.
- When the test starts, the subject will be placed on a treadmill and asked to prepare for walking. The investigator or designee should turn the treadmill on and set the incline and speed required by the protocol.
- The subject is not allowed to hold onto the railings in order to avoid measurement bias.
- The subject will be instructed, when beginning to experience pain or discomfort, to inform the investigator by saying a short word (eg, “pain” or “hurts”), and the investigator will record the distance from walking start to the pain appearance (initial claudication distance).
- The subject will then continue walking and then inform the investigator by saying a short word (eg, “done”) when he can no longer continue walking and needs rest. The investigator will record the distance from walking start to the point where the subject is unable to walk anymore (absolute claudication distance).
- The signal words should be agreed with the subject and investigator in advance of the test to avoid wasting time during the test.
- The distance walked by patient during incline and speed set up might be neglected.
- As much as possible, the same assessor should be responsible for treadmill test results assessment at a given site.
- As much as possible, assessor change throughout the study should be avoided.

9.1.7.2 SF-36

The SF-36 is a 36-item, patient-reported measure of health-related quality of life. The SF-36 has been extensively evaluated and tested with a variety of populations and is able to distinguish between groups of varying health quality-of-life status in clinical trials [22,23]. The SF-36 consists of 8 sections (vitality, physical functioning, bodily pain, general health perceptions,

physical role functioning, emotional role functioning, social role functioning, and mental health) that are the weighted sums of the questions in each health domain. Each scale is directly transformed to a 0 to 100 scale on the assumption that each question carries equal weight. The lower the score, the more disability, and the higher the score, the less disability, ie, a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability.

A validated language-specific version of the SF-36 will be available for each participating country; patients should be provided with an SF-36 in a language in which they are fluent. Patients should complete the SF-36 at Visits 1, 5 and 8 (or End-of-Treatment) before any study-related procedures are performed. The investigator must check that all questions are answered.

9.1.8 Documentation of Concomitant Procedures and Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over-the-counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded in the eCRF. In addition, concomitant procedures will be collected and recorded in the eCRF.

9.1.9 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the screening examination, according the judgment of the investigator.

9.1.10 Ultrasound Color Duplex Imaging

Ultrasound color duplex imaging will be used at Screening for verification of the PAD diagnosis and exclusion of other pathology that may lead to peripheral artery occlusion. The location of arterial narrowing and occlusion will also be identified, and an aortoiliac or femoropopliteal lesion will be documented in the patient's medical chart and case report form. The examination will be carried out on certified equipment by a qualified specialist of ultrasonic diagnostics in accordance with the generally accepted methodology. The examination will be performed according to local routine practice. Results (at a minimum, paper conclusion) should be stored together with other source documents.

Ultrasound duplex imaging of the lower limb vessels is to be performed by the standard method.

Special preconditioning of the subject is not required. The subject will remove clothing from the lower limbs and then will be placed on the bed in the supine position. The subject should be advised to wear an underwear which opens inguinal folds, which is where the duplex imaging begins.

After placing the subject on the bed and preparing him/her for the examination, the investigator will apply ultrasound gel on the probe and run the probe along the main vessels of the leg. Both legs will be examined individually. If necessary, the subject may be asked to stand up to continue examination in the upright position.

Besides the standard parameters, the level (segment) of the vessel lesion (aortoiliac or femoropopliteal) and the lesion type (occlusion or stenosis) will be recorded.

The ankle brachial index (ABI) assessment will be performed by measuring the systolic blood pressure (BP) from both brachial arteries, posterior tibial arteries, and both dorsalis pedis arteries.

Smoking and alcoholic or soft drinks are not allowed for patients during at least 2 hours before the procedure. The subject should be physically and emotionally relaxed for at least 30 minutes before the procedure. The measurement is to be performed in the supine position after the rest in this position for 10 minutes.

The blood pressure cuff should be placed as follows: right arm, left arm, then both lower limbs in any order.

The lower edge of the cuff should be at 3 to 5 cm superior to the elbow bend or 3 to 5 cm superior to the ankle-joint. The cuff should be inflated to stop the blood flow in the brachial artery or in the tibia, respectively. The cuff should then be slowly deflated and the pressure recorded when the first pulse wave appears. The systolic blood pressure of the artery at the appearance of the first pulse will then used for calculations.

The systolic blood pressure from upper and lower limbs should be measured by a hand-held Doppler probe on 5-10 MHz.

ABI should be calculated using the following formula:

ABI = ankle sBP/ brachial sBP

Ankle sBP is defined as the higher of two systolic BPs from a lower limb. Systolic BP of the postural tibial artery should be compared to systolic BP of the dorsalis pedis artery of the same leg, the highest value should be used for calculations. This will be repeated to determine the value for the opposite leg.

As a result, 2 ankle systolic BPs will be provided for ABI calculations.

Brachial sBP is defined as the higher of systolic BPs from both upper limbs. As a result, one brachial systolic BP will be provided for ABI calculations.

Blood pressure should be measured on both arms because of possible lesions of clavicular or axillary arteries in patients with PAD.

ABI calculations should yield in 2 values rounded to 2 decimal places. The worst (the lowest) ABI should be chosen for further investigations.

9.1.11 Procedures for Clinical Laboratory Samples

All samples will be collected under fasting conditions (at least 8 hours after the last meal) and in accordance with acceptable local laboratory procedures. The maximum volume of blood collected at any single visit will be approximately 15 mL, with an approximate total volume of blood collection over the course of the study of 45 mL.

Timing of collection for clinical laboratory testing is provided in Table 9.a and Appendix A.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Hemoglobin	Glucose	Glucose
	HbA1c (for Screening only) (a)	
	Creatinine	
Hematocrit	Total bilirubin (b)	Nitrites
Erythrocytes	Alkaline phosphatase	Erythrocytes
Thrombocytes	Albumin	Leucocytes
Leukocytes	AST	Protein
White blood cell count (d)	ALT	
	γ-glutamyl transferase (GGT)	
	Creatine kinase	
	Sodium	
	Potassium	
	Cholesterol (total, high-density lipoprotein, and low-density lipoprotein)	
	Triglycerides	
Diagnostic Screening:		
Serum		**Urine**
Human chorionic gonadotropin (hCG), female subjects (c)		hCG (female subjects)

(a) HbA1c at Screening for eligibility assessment.
(b) If values are above the normal range, then direct and indirect bilirubin will be determined.
(c) At Screening.
(d) Must include numbers of segmented neutrophils and band cells.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, and GGT should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Section 7.5 and Section 10.2.3 for the appropriate guidance on reporting abnormal liver function tests.)

If ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3).

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

9.1.12 Contraception and Pregnancy Avoidance Procedure

9.1.12.1 Male Subjects and Their Female Partners

From the signing of the informed consent, throughout the duration of the study or for 30 days after the last dose of study drug (in case of early study termination), nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list of highly effective/effective contraception (Section 9.1.12.3).

9.1.12.2 Female Subjects and Their Male Partners

From the signing of the informed consent, throughout the duration of the study or for 30 days after the last dose of study drug (in case of early study termination), female subjects of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective/effective method of contraception (Section 9.1.12.3).

In addition, they must be advised not to donate ova during this period.

9.1.12.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and

correctly). In this study, where medications and devices containing hormones are included, the acceptable methods of highly effective contraception are:

- Nonhormonal methods:
  - Intrauterine device.
  - Bilateral tubal occlusion.
  - Vasectomized partner (provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success).
- Hormonal methods:
  - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months:
    - Oral.
    - Intravaginal (eg, ring).
    - Transdermal.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months:
    - Oral.
    - Injectable.
    - Implantable.

2. Effective methods of contraception are defined as those that result in a low failure rate that may be higher than a 1% failure rate. In this study, where medications and devices containing hormones are included, the acceptable effective methods of contraception are:
   - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).
   - Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.
3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.

- No method at all.
- Use of female and male condoms together.
- Cap/diaphragm/sponge without spermicide and without condom.
- Sexual abstinence is NOT an acceptable method of contraception.

4. Subjects will be provided with information on highly effective and effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
5. During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study.
   b) Assessment of subject compliance through questions such as:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
      iv. Is there a chance you could be pregnant?
6. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), and a negative urine hCG pregnancy test at the Randomization (Baseline) Visit before receiving any dose of the study drug.

9.1.13 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 30 days after the last dose (in case of early study termination) should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of the study drug, eg, after Visit 1 or within 30 days of the last dose of the study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject or female partner of the male subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.14 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. A copy of the ECG trace should be kept with the subject's study source documentation.

9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is withdrawn at the Screening Visit, the investigator should complete the eCRF.

The data to be collected in eCRF for Screen Failures as a minimum: subject number and initials, date of informed consent, demographic data, inclusion/exclusion criteria, PTEs/SAEs, date of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria <specify reason>.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.
- Other <specify reason>.

Subject identification numbers assigned to subjects who fail Screening should not be reused.

9.1.16 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

During the IV Treatment Period, the daily IV infusions will be recorded on an infusion log. The following data will be recorded:

- Kit details.
- Infusion date.
- Start time.
- Stop time.
- Initials of person administering IMP.
- Infusion successfully completed; yes or no.
- Comments.

During the Oral Treatment Period, the investigator must check subject compliance by counting the number of returned tablets at time points specified in the clinical study overview. Subjects will be required to bring the dispensed study medication bottles to each site visit. All cases of lost or damaged tablets must be documented.

Treatment compliance will be calculated by the investigator at Visits 3, 4, and 5 using the formula:

Compliance in % =

100 × (number of tablets dispensed – number of tablets returned) / (expected number of tablets to be taken)*

Whereby ***expected number of tablets to be taken =***

6 × (date of last dose – date of first dose + 1) - 2 × (3 - time of last dose) - 2 × (time of first dose - 1)

Where ***time of first/last dose of medication*** *equal to*

- ***1*** *for Morning dose*
- ***2*** *for Daytime dose*
- ***3*** *for Evening dose*

* Returned tablets include lost/damaged tablets, those that were expected to be returned.

These data will subsequently be recorded in the eCRF by site personnel.

Subjects will be considered to be non-compliance with study medication if they miss > 20% of doses required for the visit period, or to take more than 120% of the doses for the treatment period

since last visit. If these criteria for noncompliance are met protocol deviation is to be reported. Any detected overdose (Section 8.1.4) must be reported on an Overdose page of the eCRF.

In case of a compliance deviation, all subjects should be reinstructed about the dosing requirements during study contacts. The authorized study personnel conducting the re-education must document the process in the source records.

If a subject is persistently noncompliant with the study drug (eg, compliance for 2 subsequent visits is outside of 80% to 120%), it should be reported as a significant protocol deviation and may be appropriate (based on investigator's judgment) to withdraw the subject from the study.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening Period

Screening is considered to be started from the moment of informed consent form signed. Subjects will be screened 1 to 2 weeks before Randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.15 for procedures for documenting screening failures.

The following will be recorded or conducted at Screening (Visit 0):

- Informed consent.
- Demographics.
- Medical history and concurrent medical conditions.
- Medication history.
- Concomitant medications.
- PTEs.
- Physical examination.
- Vital signs.
- Smoking status and physical activity.
- 12-lead ECG procedure.
- Clinical laboratory tests.
- Serum hCG pregnancy test (for female subjects of childbearing potential only) and oral confirmation of menses in the month before first dosing (no delayed menses).
- Ultrasound color duplex imaging.

- Treadmill testing (up to 2 tests are to be done during the screening period. The second treadmill test should be repeated in ≥1 week (ie, 7 days) after the first treadmill test. It is acceptable for the second treadmill test to be completed on the day of randomization).
- Inclusion/exclusion criteria.

9.3.2 Randomization (Baseline), Day 1 Visit 1

Randomization will take place on Day 1.

The following will be recorded or conducted at Randomization (Visit 1):

- Inclusion/exclusion criteria.
- SF-36 (before any procedure).
- PTEs.
- Smoking status and physical activity.
- Treadmill testing (this may be the second test within screening period to verify that results of both tests are within 25%) (Sections 7.2 and 9.1.7.1; Appendix A).
- Urine pregnancy test (for female subjects of childbearing potential only).
- Assessment of subject compliance with contraception requirements.
- Physical examination.
- Vital signs.
- Weight and height.
- Concomitant medications.
- Medication history.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IRT system, as described in Section 8.2.

9.3.3 Infusion (IV) Treatment Period

Following Randomization, subjects will enter the IV Treatment Period (Day 1 Visit 1 until Day 14 Visit 2), during which they receive daily infusions of actovegin or placebo (up to a maximum of 14 infusions).

IP Infusions must be performed in the investigational site under medical supervision. During the first 15 min of the first infusion such supervision should be carried out by Investigator (or designated physician) in order to find out promptly possible allergic reactions and to be able to take urgent measures to prevent or treat them.

The following will be recorded during the IV Treatment Period from Day 1 to Day 13:

- AEs (at Day 1 after the first infusion). Starting on Day 2, AEs should be checked before (since previous infusion) and after the infusion.

9.3.4 End-of-IV Treatment, Day 14, Visit 2

The End-of-IV treatment is defined as the day of the last infusion (Day 14) and before the initiation of oral treatment. The assessments required at this visit should take place following the final infusion. For subjects who terminate the study before completing the IV treatment period, the Early Termination Visit will be Visit 5.

The End-of-IV visit and subsequent switch to oral treatment may either be performed while the subject is still hospitalized or upon discharge in accordance with the subject's needs.

The following will be recorded or conducted at the End-of-IV treatment visit (Visit 2):

- AEs (before infusion [since last visit] and after the infusion).
- Concomitant medications.
- Smoking status and physical activity.
- Treadmill testing.
- Urine pregnancy test (for female subjects of childbearing potential only).
- Assessment of subject compliance with contraception requirements.
- Study drug dispensation for oral treatment.

9.3.5 Oral Treatment Period

The Oral Treatment Period is defined as the period from the day after the last infusion until 12 weeks after Randomization (Days 15 to 84). During the Oral Treatment Period, the subject will visit the site on Day 42 (±2 days) Visit 3 and Day 70 (±2 days) Visit 4.

The following will be recorded or conducted during the Oral Treatment Period (Visits 3 and 4):

- AEs (since last visit).
- Concomitant medications.
- Smoking status and physical activity.
- Urine pregnancy test (for female subjects of childbearing potential only).
- Assessment of subject compliance with contraception requirements.
- Study drug dispensation for oral treatment.
- Return study drug for oral treatment.
- Study drug compliance check.

9.3.6 End-of-Oral Treatment, Day 84, Visit 5 /Early Termination Visit

The End-of-Oral Treatment Visit will occur on the last day of oral dosing at Week 12 (Day 84 ±2 days). This will also be the Early Termination Visit for subjects who terminate the study before completing the Oral Treatment Period.

The following will be recorded or conducted at the End-of-Oral Treatment Visit (Visit 5):

- AEs (since last visit).
- Physical examination.
- Vital signs.
- Weight.
- Concomitant medications.
- Smoking status and physical activity.
- SF-36 (before any procedure).
- Clinical laboratory tests.
- Urine pregnancy test (for female subjects of childbearing potential only).
- Assessment of subject compliance with contraception requirements.
- Treadmill testing.
- Return study drug for oral treatment.
- Study drug compliance check.

9.3.7 Follow-up Period

A 12-week Follow-up Period will begin the first day after the End-of-Oral Treatment Visit (Visit 5), during which, subjects will visit the site every 4 weeks at Day 112 (±5 days) Visit 6 and Day 140 (±5 days) Visit 7.

The following will be recorded during each Follow-Up visit (Visits 6 and 7):

- AEs (since last visit).
- Concomitant medications.
- Smoking status and physical activity.
- Urine pregnancy test (for female subjects of childbearing potential only).
- Assessment of subject compliance with contraception requirements.

9.3.8 Final Follow-up Visit/Early Termination Visit

The Final Follow-up Visit will occur on the last day of the Follow-up Period (Day 168 ±2 days). This will also be the Early Termination Visit for subjects who terminate the study during the Follow-up Period.

The following will be recorded or conducted at the Final Follow-up Visit (Visit 8):

- AEs (since last visit).
- Physical examination.
- Vital signs.
- Weight.
- Concomitant medications.
- Smoking status and physical activity.
- Clinical laboratory tests.
- Urine pregnancy test (for female subjects of childbearing potential only).
- Assessment of subject compliance with contraception requirements.
- Treadmill testing.
- SF-36 (before any procedure).

For all subjects receiving study drug, the investigator must complete the End of Study eCRF page.

9.3.9 Post Study Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but before the administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG retest and/or continued monitoring of an abnormal value or finding is not

considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious, or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs /serious PTEs:

- If the subject experiences changes in intensity of an AE/serious PTE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled before the signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the

worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 AESIs

AESIs in this study include the following.

- Hypersensitivity:

  Hypersensitivity or AEs relating to hypersensitivity.
- Transmission of bovine infective agents:

  Prion-associated disorders, iatrogenic infections, suspected transmission or transmission of an infectious agent via product, and encephalopathy.
- Transmission of infectious agents – lack of sterility:

  All AEs of infections.
- Off-label use as an athletic performance enhancer:

  Intentional product misuse.

10.1.6 Intensity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.

10.1.13 Outcome

- Recovered/resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Study Visit 1) or until screen failure. For subjects who discontinue before study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug (Study Visit 1). Routine collection of AEs will continue until Study Visit 8.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked.

Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject identification number.
- Investigator's name.
- Name of the study drug(s)
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.10 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax or e-mail it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, Ethics Committees, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the EMA, investigators, and ethics committee, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the study. The study site also will forward a copy of all expedited reports to his or her ethics committee in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. All eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last

approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before the unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted before the unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The full analysis set (FAS) will include all subjects who were randomized, received at least 1 dose of study drug, and have at least 1 valid post-baseline value for assessment of primary endpoint. In FAS efficacy summaries and analyses, subjects will be analyzed by the treatment to which they were randomized.

The Safety Set will include all subjects who were randomized and received at least 1 dose of double-blind study medication. In safety summaries, subjects will be analyzed according to the treatment they received. In the event that a subject receives more than 1 treatment, the actual treatment will be defined as the one that is used most frequently. If the 2 most common treatments are used with equal frequency, then the randomized treatment will be used as the actual treatment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics Analysis of Demographics and Other Baseline Characteristics

Baseline characteristics will be listed and summarized for demographics (sex, age, and race), physical examination, and medical history including psychiatric history, smoking history, diabetic status, and concomitant medications.

Baseline values for efficacy and safety parameters will be in the standard tables summarizing data per visit; however, baseline efficacy data will also be presented separately based on the all subjects randomized.

For continuous variables, comparability of treatment groups will be assessed using an analysis of variance with treatment and center as factors. For discrete variables, comparability will be assessed using the Cochran-Mantel-Haenszel general association test, stratified by center. The p-values will be displayed as descriptive statistics of comparability.

13.1.3 Efficacy Analysis

The primary and secondary endpoints will be analyzed in randomized patients who received at least one dose of study drug.

Percent change from Baseline in ICD and change from Baseline in SF-36 will be analyzed using a mixed model for repeated measurements (MMRM) analysis of covariance with treatment, center, sex, age group, visit, treatment-by-visit interaction as fixed effects, Baseline as covariate,

and subject as a random effect. Comparisons between actovegin and placebo will be performed on all assessment points. Based on a missing at random assumption, this analysis will be performed using observed case data only. The effect at each time point for each treatment is allowed to vary freely and an unstructured covariance matrix is assumed.

Proportion of subjects having rest pain and proportion of patients having revascularization procedures will be analyzed at all time points by logistic regression adjusting for treatment.

13.1.4 Safety Analysis

13.1.4.1 AEs

AEs will be reported throughout the study.

The definition of treatment-emergent AEs will be provided in the SAP. AEs will be coded using MedDRA and will be summarized by system organ class and preferred term in the core treatment period and entire study.

AEs that were reported more than once by a subject during the same period will be counted only once for that subject and period at the maximum severity.

13.1.4.2 Clinical Evaluations

Absolute values and changes from Screening/Baseline in clinical safety laboratory tests, vital signs, and weight will be summarized for each treatment group using descriptive techniques. Values outside normal ranges and potentially clinically significant values will be flagged and tabulated. Physical examination findings will also be summarized for each treatment group.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The primary endpoint of change from Baseline in ICD (initial claudication distance) is the most clinically important parameter for evaluation of effectiveness of Fontaine Stage II PAD treatment; this endpoint is recommended in the EMA guideline "Note for guidance on clinical investigation of medicinal products for treatment of peripheral arterial occlusive disease." Although several trials about actovegin have been done [16-19], [24], none of them have the same primary endpoint as the proposed study. Additionally, the study design, study duration, primary endpoint, treadmill test setting and/or target patients is also different in the proposed study.

The sample size justification is based on published data for Naftidrofuryl study [25]. This study is a randomized, double-blind, placebo-controlled, parallel-group study, including 154 patients with Stage II intermittent claudication. The 90-day examination data of Naftidrofuryl study is close to our 12-week treatment duration. The study design, measurement time, targeted patients and treadmill test setting for [25] are similar to the proposed study. For the Naftidrofuryl study,

the primary endpoint change from Baseline in ICD is similar to our primary endpoint (percent change from Baseline in ICD), the difference in percent change from Baseline in ICD between Naftidrofuryl and placebo is approximately 28%, while the corresponding pooled standard deviation is approximately 85%.

Two-sample t test with a 0.05 two-sided significance level is used for sample size calculation. Since the allocation ratio is 1:1, the sample size per each arm is calculated by the formula below [26,27]:

$$n_1 = n_2 = \frac{(\delta_1{}^2+\delta_2{}^2)(z_{1-\frac{\alpha}{2}}+z_{1-\beta})^2}{\Delta^2},$$

where n_i is the sample size without drop-out for group i (i=1,2), δ_i is the assumed standard deviation for group i (i=1,2), α is the two-sided significance level, 1-β is the power, Δ is the difference in population means, and $z_{1-\alpha/2}$ and $z_{1-\beta}$ are the z-values.

Assuming $\delta_1 = \delta_2$ =85% and Δ=28% for the percent change from Baseline in ICD, a total of 292 subjects (146 per each arm) is sufficient to achieve at least 80% power. Considering 20% drop-out rate, a total of 366 patients (183 per each arm) should be randomized in the study.

Table 13.a shows the sensitivity test for sample sizes (with and without drop-out) required for different values of power (from 70% to 95%) while 85% SD, 28% mean difference, 0.05 significance level and 20% drop-out rate are assumed.

Table 13.a Sample Sizes Under Different Values of Power

Power (1-β)	70%	75%	80%	85%	90%	95%
Significant level (α)	0.05	0.05	0.05	0.05	0.05	0.05
Mean difference (Δ=m1-m2)	28%	28%	28%	28%	28%	28%
Standard deviation (δ_i)	85%	85%	85%	85%	85%	85%
n_1 (without drop-out)	115	129	146	167	195	241
Drop-out rate	20%	20%	20%	20%	20%	20%
N_1 (considering drop-out)	144	162	183	209	244	302
N (total sample size)	288	324	366	418	488	604

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by the sponsor or its designee, the Contract Research Organization, and by the ethics committee.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and ethics committee, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and ethics committee, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A protocol deviation form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol. Significant protocol violations are entered on the eCRF.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 Ethics Committee Approval

Ethics committees must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective ethics committee. If any member of the ethics committee has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective I ethics committee for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local ethics committee for approval. The ethics committee's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The ethics committee approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification, no protocol activities, including Screening, may occur.

Study sites must adhere to all requirements stipulated by their respective ethics committee. This may include notification to the ethics committee regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective ethics committee, and submission of the investigator's final status report to the ethics committee. All ethics committee approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if

applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and ethics committee approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the ethics committee and the sponsor before use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the ethics committee. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a pen with blue or black ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and before the subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, Ministry of Health of Russian Federation, Food and Drug Administration, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate ethics committee to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

	Screening Period	Treatment Period							Follow- up Period		
		Randomization (Baseline)	Infusion Treatment (IV)			Oral Treatment					
Day	Day -7-14 to -1	Day 1	Start of IV treatment Day 1	IV treatment Day 2-Day 13	End of IV treatment Day 14	V2+28 ±2 days (Day 42)	V3+28 ±2 days (Day 70)	End of treatment V4+14 ±2 days (Day 84) (a)	Interim Follow-up (4 weeks interval ±5 days) (Day 112)	Interim Follow-up (4 weeks interval ±5 days) (Day 140)	Final Follow-up V7+28 ±2 days (Day 168) (b)
Visit No.	V0	V1	V1		V2	V3	V4	V5	V6	V7	V8
Informed consent	X										
Inclusion/ exclusion criteria	X	X									
Demographics	X										
Medication history	X	X									
Medical history and concurrent medical conditions	X										
Smoking status and physical activity	X	X			X	X	X	X	X	X	X
Pretreatment events	X	X									
AEs			X (c)	X (c)	X (c)	X	X	X	X	X	X
Physical examination	X	X						X			X
Vital signs	X	X						X			X
Height and weight (d)		X						X			X
Concomitant medications	X	X			X (e)	X	X	X	X	X	X
12-lead ECG	X										
Clinical laboratory tests	X							X			X
Pregnancy test (f) and assessment of subject compliance with contraception requirements.	X (g)	X			X	X	X	X	X	X	X

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screening Period	Treatment Period							Follow- up Period		
		Randomization (Baseline)	Infusion Treatment (IV)			Oral Treatment					
Day	Day -7-14 to -1	Day 1	Start of IV treatment Day 1	IV treatment Days 2-13	End of IV treatment Day 14	V2+28 ±2 days (Day 42)	V3+28 ±2 days (Day 70)	End of treatment V4+14 ±2 days (Day 84) (a)	Interim Follow-up (4 weeks interval ±5 days) (Day 112)	Interim Follow-up (4 weeks interval ±5 days) (Day 140)	Final Follow-up V7+28 ±2 days (Day 168) (b)
Visit No.	V0	V1	V1		V2	V3	V4	V5	V6	V7	V8
Glycosylated hemoglobin HbA1c	X										
Treadmill test	X	X (h)			X (e)			X			X
Ultrasound color duplex imaging	X										
SF-36		X						X			X
Dispense study drug for oral treatment					X (e)	X	X				
Return study drug for oral treatment						X	X	X			
Study drug compliance check						X	X	X			

V=visit.
(a) Early Termination Visit for subjects who terminate the study before completing the Oral Treatment Period.
(b) Early Termination Visit for subjects who terminate the study during the Follow-up Period.
(c) On Day 1 Visit 1, AEs should be checked after infusion. Starting on Day 2, AEs should be checked before (since previous infusion) and after the infusion.
(d) Height and weight will be measured at V1. Only weight will be measured at V5 and V8.
(e) Following the final infusion.
(f) Female subjects of childbearing potential only. Serum pregnancy test will be performed at Screening visit. Urine pregnancy test will be performed at all other visits.
(g) Assessment of compliance with contraception requirements not needed at this visit.
(h) The time interval from the first test must be of ≥1 week (ie, 7 days).

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate ethics committee that conform to ICH and local regulatory requirements.
6. Ensure that the ethics committee will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the ethics committee all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the ethics committee, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the ethics committee. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours. The investigator should also comply with the applicable regulatory requirements related to the reporting of adverse reactions to the Regulatory Authority and Ethics Committee.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), ethics committee, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and ethics committee and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) ethics committee;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.
24. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective or effective contraception (as defined in the informed consent) from Screening throughout the duration of the study or for 30 days after the last dose (in case of early study termination). If a subject is found to be pregnant during study,

study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

25. Male subjects agree to use barrier method of contraception (condom with or without spermicide) (as defined in the informed consent) from signing the informed consent throughout the duration of the study or for 30 days after the last dose (in case of early study termination). If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- Ethics committees.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 04 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Revised number of participating sites and countries.

The primary change occurs in Section 6.1 Study Design.

Initial wording:	Study Design: This is a randomized, multicenter, parallel group, double-blind, placebo-controlled phase 3b study to evaluate the efficacy and safety of actovegin 12-week treatment given intravenously and subsequently orally in subjects with peripheral arterial disease (PAD) Fontaine Stage IIB. A total of 366 subjects with PAD Fontaine Stage IIB will be enrolled in approximately 15 to 20 sites in 5 countries (Russia, Ukraine, Belarus, Kazakhstan, and Georgia)
Amended or new wording:	Study Design: This is a randomized, multicenter, parallel group, double-blind, placebo-controlled phase 3b study to evaluate the efficacy and safety of actovegin 12-week treatment given intravenously and subsequently orally in subjects with peripheral arterial disease (PAD) Fontaine Stage IIB. A total of 366 subjects with PAD Fontaine Stage IIB will be enrolled in approximately ~~15~~ **17** to ~~20~~ **25** sites in ~~5~~ **3** countries (Russia, ~~Ukraine, Belarus,~~ Kazakhstan, and Georgia).

Rationale for Change:

To revise the numbers of study sites and countries participating in the study.

Section 2.0 STUDY SUMMARY (Study Design and Number of Sites) also includes this change.

Change 2: Clarified inclusion criterion #11.

The primary change occurs in Section 7.1 Inclusion Criteria.

Added text: 11. The subject has a history of stable PAD therapy for at least 2 weeks before Screening **and is not newly diagnosed with PAD**.

Rationale for Change:

To clarify inclusion criterion # 11 that the subject must not be newly diagnosed with PAD.

Section 2.0 STUDY SUMMARY (Main Criteria for Inclusion) also includes this change.

Change 3: Clarified early discontinuation procedures.

The primary change occurs in Section 7.6 Procedures for Discontinuation or Withdrawal of a Subject.

Added text: The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit at the earliest possible date. **The Early Termination Visit for subjects who discontinue the study before completing the Oral Treatment Period will be identical to Visit 5. The Early Termination Visit for subjects who discontinue the study after completing the Oral Treatment Period will be identical to the Final Follow-up visit. The Follow-up Period is not required for subjects who discontinue the study early.** Discontinued or withdrawn subjects will not be replaced.

Rationale for Change:

To clarify procedures for subjects who discontinue the study early.

Change 4: Clarified that subjects should continue companion medications for peripheral arterial disease (PAD) and prevention of cardiovascular events.

The primary change occurs in Section 8.1.1.2 Companion Medication.

Initial wording: Subjects may continue their current treatment for PAD and for prevention of cardiovascular events.

Amended or new wording: Subjects ~~may~~ **should** continue their current treatment for PAD and for prevention of cardiovascular events.

Rationale for Change:

To clarify that subjects should continue companion medications for PAD and prophylaxis of cardiovascular events.

Change 5: Specified minimum infusion duration.

The primary change occurs in Section 8.1.3.1 IV Treatment Period (Week 0 to 2)

Added text: The infusion rate will be about 2 mL per minute (40 to 50 drops/minute). **Total infusion duration should not be less than 112 minutes.**

Rationale for Change:

To specify the minimum duration of infusion.

Change 6: Corrected timing of oral treatment period.	
The primary change occurs in Section 8.1.3.2 Oral Treatment Period (Week 3 to 12)	
Initial wording:	8.1.3.2 Oral Treatment Period (Week 2 to 12)
Amended or new wording:	8.1.3.2 Oral Treatment Period (Week ~~2~~ **3** to 12)
Rationale for Change: To correct the beginning of the oral treatment period from Week 2 to Week 3.	
Change 7: Deleted instruction to collect incorrect demographic information.	
The primary change occurs in Section 9.1.2 Demographics, Medical History, and Medication History Procedure.	
Initial wording:	Demographic information to be obtained will include date of birth, sex, race as described by the subject, height, weight, and smoking status of the subject at Screening.
Amended or new wording:	Demographic information to be obtained will include date of birth, sex, **and** race as described by the subject~~, height, weight, and smoking status of the subject~~ at Screening.
Rationale for Change: To delete collection of incorrect demographic information.	
Change 8: Specified timing of height and weight assessments.	
The primary change occurs in Section 9.1.4 Weight and Height.	
Added text:	Weight and height of subjects should be measured while wearing indoor clothing and no shoes. Values are to be reported to 1 decimal place. **Height will be measured at V1. Weight will be measured at V1, V5, and V8.**
Rationale for Change: To clarify the timing of height and weight assessments.	

Change 9: Clarified that questionnaires should be provided to patients in a language in which they are fluent.

The primary change occurs in Section 9.1.5 Smoking Status and Physical Activity.

Initial wording:	Patients should be provided with the Physical Activity Questionnaire in their native language
Amended or new wording:	Patients should be provided with the Physical Activity Questionnaire in ~~their native~~ **a** language **in which they are fluent.**

Rationale for Change:

To clarify that questionnaires provided to patients should be in a language in which they are fluent.

Section 9.1.7.2 SF-36 also includes this change (with reference to the SF-36).

Change 10: Clarified fasting conditions and revised maximum blood volume collected.

The primary change occurs in Section 9.1.11Procedures for Clinical Laboratory Samples.

Initial wording:	All samples will be collected under fasting condition and in accordance with acceptable local laboratory procedures. The maximum volume of blood collected at any single visit will be approximately 10 mL, with an approximate total volume of blood collection over the course of the study of 30 mL.
Amended or new wording:	All samples will be collected under fasting condition**s (at least 8 hours after the last meal)** and in accordance with acceptable local laboratory procedures. The maximum volume of blood collected at any single visit will be approximately ~~10~~ **15** mL, with an approximate total volume of blood collection over the course of the study of ~~30~~ **45** mL.

Rationale for Change: To specify that fasting conditions are considered as at least 8 hours after the last meal, and to revise the maximum amount of blood collected at each visit and over the entire course of the study.

Change 11: Specified details of white blood cell count.

The primary change occurs in Table 9.a Clinical Laboratory Tests Clinical Laboratory Tests.

Description of change: A footnote was added for white blood cell count:

- White blood cell count **(d)**
  - **(d) Must include numbers of segmented neutrophils and band cells.**

Rationale for Change: To specify that the white blood cell count should include numbers of segmented neutrophils and band cells.

Change 12: Added requirement to document lost or damaged tablets and defined the nature of returned tablets.

The primary change occurs in Section 9.2 Monitoring Subject Treatment Compliance.

Added text: During the Oral Treatment Period, the investigator must check subject compliance by counting the number of returned tablets at time points specified in the clinical study overview. Subjects will be required to bring the dispensed study medication bottles to each site visit. **All cases of lost or damaged tablets must be documented.**

Treatment compliance will be calculated by the investigator at Visits 3, 4, and 5 using the formula:

Compliance in % =

*100 × (number of tablets dispensed – number of tablets returned*****) / (expected number of tablets to be taken)*

Whereby ***expected number of tablets to be taken =***

6 × (date of last dose – date of first dose + 1) - 2 × (3 - time of last dose) - 2 × (time of first dose - 1)

Where ***time of first/last dose of medication*** *equal to*

- ***1*** *for Morning dose*
- ***2*** *for Daytime dose*
- ***3*** *for Evening dose*

*** Returned tablets include lost/damaged tablets, those that were expected to be returned.**

Rationale for Change: To include a requirement to document lost or damaged tablets and to define the nature of returned tablets.

Change 13: Added AESIs.

The primary change occurs in Section 10.1.5 AESIs.

Added text: **10.1.5 AESIs**

AESIs in this study include the following.

- **Hypersensitivity:**

  Hypersensitivity or AEs relating to hypersensitivity.

- **Transmission of bovine infective agents:**

  Prion-associated disorders, iatrogenic infections, suspected transmission or transmission of an infectious agent via product, and encephalopathy.

- **Transmission of infectious agents – lack of sterility:**

  All AEs of infections.

- **Off-label use as an athletic performance enhancer:**

  Intentional product misuse.

Rationale for Change: To include AESIs in the protocol.

Change 14: Clarified method of signing the informed consent.

The primary change occurs in Section 15.2 Subject Information, Informed Consent, and Subject Authorization.

Initial wording:	The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink.
Amended or new wording:	The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using **a pen with** blue or black ~~ballpoint~~ ink.

Rationale for Change: To clarify that the informed consent should be signed with a pen.

Change 15: Removed specific assessments from the Schedule of Study Procedures.	
The primary change occurs in Appendix A Schedule of Study Procedures.	
Description of change:	The following assessments were removed for the start of IV treatment, Day 1: • Smoking status and physical activity. • Concomitant medications. • Pregnancy test and assessment of subject compliance with contraception requirements.
Rationale for Change: These assessments will be performed at the screening and baseline visits.	

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	20-Feb-2019 18:17 UTC
	Clinical Science Approval	20-Feb-2019 20:51 UTC
	Medical Affairs Approval	22-Feb-2019 12:32 UTC