3.4 Corporate Identification

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

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.

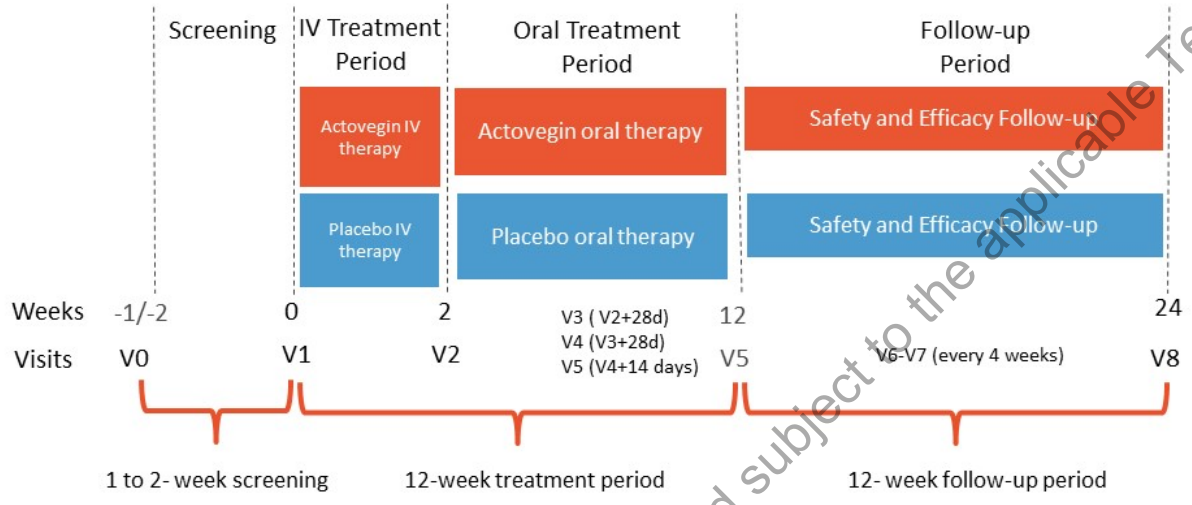
Subjects with a history of stable intermittent claudication with symptoms that have been present continuously for at least 6 months at the time of Screening. A diagnosis of PAD (ICD of <200 meters) will be confirmed by ultrasound color duplex imaging and treadmill test.

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.

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,

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.

- 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:

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

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.

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

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

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).

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

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.

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.

- 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.

- 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.

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).

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.

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.

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.

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.