



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

SAP Approve Date: 11 November 2019

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Actovegin-3001

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

PHASE 3

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PPD

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1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

Study 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

Reviewers/Approvals:

PPD



PPD



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3.0 LIST OF ABBREVIATIONS

ACD	absolute claudication distance
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
GGT	γ -glutamyl transferase
IC	intermittent claudication
ICD	initial claudication distance
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IP	investigational product
IV	intravenous
LFT	liver function tests
LDH	lactate dehydrogenase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
PAD	peripheral arterial disease
PD	pharmacodynamics
PK	pharmacokinetics
PPS	per-protocol set
QOL	quality-of-life
PRO	patient-reported outcome
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SF-36	36-item Short Form Survey
TID	3 times daily
TLGs	tables, listings, and graphs
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

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

4.2 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.

4.3 Safety Objectives

- To evaluate the safety of actovegin compared with placebo.

4.4 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.

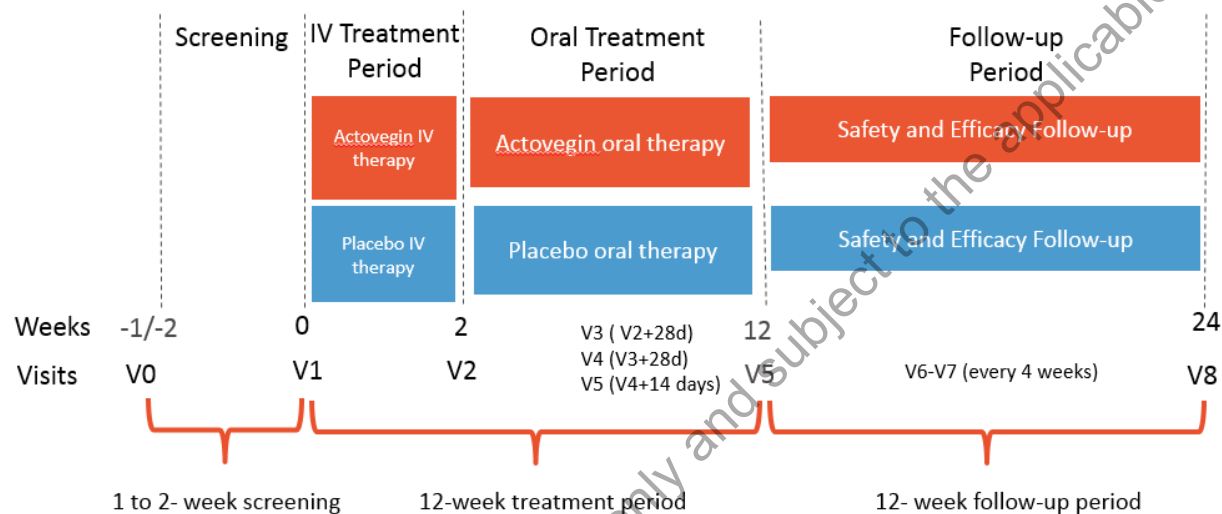
Subjects with a history of stable intermittent claudication with symptoms that have been present continuously for at least 6 months at the time of Screening. A diagnosis of PAD (ICD of < 200 meters) will be confirmed by ultrasound color duplex imaging and treadmill test.

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 4.4](#). A schedule of assessments is listed in [Appendix A](#).

Figure 4.4 Schematic of Study Design



V=visit

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

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

5.2 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.

5.3 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 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 [1-5], 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 subjects is also different in the proposed study.

The sample size justification is based on published data for Naftidrofuryl study [6]. This study is a randomized, double-blind, placebo-controlled, parallel-group study, including 154 subjects 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 subjects and treadmill test setting for [6] 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 [7, 8]:

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

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

Assuming $\sigma=85\%$ and $\Delta=28\%$ 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 subjects (183 per each arm) should be randomized in the study.

Table 6 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 6 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 ($\Delta=m_1-m_2$)	28%	28%	28%	28%	28%	28%
Standard deviation (σ)	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

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS[®] Version 9.4, or higher.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at $\alpha=0.05$ significance level unless otherwise stated. P-values will be rounded to 4 decimal places prior to assessment of statistical significance.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Baseline values are defined as the last observed value before the first dose of study medication.

All subgroup analyses will be performed in an exploratory manner and are not powered or designed to detect differences in subgroups. Categories within a subgroup will only be analyzed if, within the study groups, the category contains at least 5% of the total number of subjects in the subgroup. If this criterion is not met, a page for the category will be displayed stating: "Analysis was not performed as this category does not contain at least 5% of the number of subjects in the subgroup within each study group." Nevertheless, for all subgroups at least descriptive statistics will be presented.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the study medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Study Visit Windows

All data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

7.1.4 Conventions for Missing Adverse Event Dates

Adverse events with start dates that are completely or partially missing will be imputed as follows:

- If month and year are known but day is missing
 - If month and year are the same as month and year of first dose date, then impute to first dose date
 - If month and year are different than month and year of first dose date, then impute to first date of the month
- If year is known but day and month are missing
 - If year is same as year of 1st dose date, then 1st dose date will be used instead
 - If year is different than year of 1st dose date, then 1st of January of the year will be imputed.

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date.

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

- If “ongoing” is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
 - If YYYY < year of last dose, then 31st of December will be imputed
 - If YYYY = year of last dose, then 31st of December will be imputed
 - If YYYY > year of last dose, then 1st of January will be imputed
- If all are missing, no imputation is necessary. The event will be considered “ongoing”.

If an AE is ongoing, AE stop date could be missing. Otherwise, AE stop date could be imputed per above rules. If a subject dies during the study and AE stop date is missing, then the death date will be used for AE stop date. After the imputation, all the imputed stop dates are compared with the start dates to ensure the stop date does not occur before the start date. If the imputed stop date occurs prior to the start date, then the imputed stop date will be the same as the start date.

The imputed dates will not be populated on the data listing, they are used for derivation purpose only. The actual and incomplete date will be on the data listing.

7.1.5 Conventions for Missing Concomitant Medication Dates

Concomitant medications with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known, but day is missing, then impute day to first of the month
- If year is known, but day and month are missing, then 1st of January of the year will be imputed

Concomitant medications with stop dates that are completely or partially missing will be analyzed as follows:

- If “ongoing” is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
 - If YYYY < year of last dose, then 31st of December will be imputed
 - If YYYY = year of last dose, then 31st of December will be imputed
 - If YYYY > year of last dose, then 1st of January will be imputed
- If all is missing, no imputation is necessary. It will be considered “ongoing”.

If a concomitant medication is ongoing, the stop date could be missing. Otherwise, concomitant medications stop date could be imputed per above rules. If a subject dies during the study and the concomitant medication stop date is missing, then the death date will be used for the stop date. After the imputation, all the imputed stop dates are compared with the start dates to ensure the stop date does not occur before the start date. If the imputed stop date occurs prior to the start date, then the imputed stop date will be the same as the start date.

The imputed dates will not be populated on the data listing, they are used for derivation purpose only. The actual and incomplete date will be on the data listing.

7.2 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 **Per-Protocol Set (PPS)** will consist of all subjects in the FAS who have no significant protocol deviations as presented in Section 7.3. These criteria for exclusion of subjects from the PPS will be reviewed, approved and documented (in a separate document) prior to database lock and unblinding as part of the blinded data review. Any changes to these criteria after approval of the SAP will be documented and approved in a separate document prior to database lock and unblinding. The PPS will only be used for supportive analyses for primary and key secondary efficacy endpoints.

The **Safety Set (SAF)** 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. If 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.

7.3 Disposition of Subjects

The table of disposition of subjects includes the number of subjects in the following categories: subjects enrolled, subjects randomized, subjects treated, subjects completed treatment, subjects completed study, subjects discontinued of study, and primary reason for discontinuation study. Percentages will be presented.

A listing will present data concerning subject disposition.

The significant protocol deviations captured on the eCRF or derived from programming will be summarized/listed by the standard protocol deviation (PV) terms (see below). The significant protocol deviation criteria will be reviewed, approved and documented (in a separate document) prior to database lock and unblinding as part of the blinded data review.

Significant protocol deviation criteria will be based on the Actovegin-3001 Clinical Study Protocol Deviations Management Plan (FORM-0002660):

Standardized Protocol Deviation Terms (eCRF):

- Inclusion/exclusion criteria not met
- Missing informed consent
- Use the prohibited medications during the treatment period
- Any missed/incorrect study procedure that directly impacts the primary study objectives or subject safety
- Dispensing of incorrect treatment and/or incorrect dose of study medication
- PAD therapy is not stable

List the protocol deviations to be programmed from the clinical database (eCRF data).

Programmable listings serve as a means to identify records missing from the Significant Protocol Deviation eCRF.

Programming Protocol Deviation criteria:

- Oral drug compliance is below 80%
- Inclusion/exclusion criteria not met
- Doesn't have the primary endpoint at week 12 or at baseline
- Use the prohibited medications during the treatment period

CRO Protocol Deviation Tracking Log (CRO standard form SF-CL-10.02-01) will be used for collection of information about all (either significant and non-significant) protocol deviations revealed during the Study course.

7.4 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized for sex, age, age group (<65, ≥65 years of age), race, BL height, BL weight, and BL BMI. The table will also include a summary of study subject baseline characteristics: duration of peripheral artery disease (years), class of medications taken to treat PAD, smoking history, diabetic status, and ABI index at screening. A listing of demographics and baseline characteristics will be provided.

Baseline values for efficacy and safety parameters will be presented in the standard tables (Takeda Global Template for Common Table Shells, 25MAR2017), summarized per visit.

7.5 Medical History and Concurrent Medical Conditions

General medical history data will be presented in a summary table by SOC/PT, and in a listing by subject.

Physical examination data will be presented in a listing.

7.6 Prior and Concomitant Medications, Concomitant Procedures

Prior and concomitant medications and procedures will be coded by generic term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of subjects taking concomitant medications will be tabulated by WHO drug preferred name (generic term) from the first dose of study treatment through 30 days after the last dose of study medication.

Concomitant medications will be summarized in a table and presented in by-subject listings, separately.

The medications for the treatment of PAD will be identified by ATC code and then summarized in a table according to the following categories and corresponding preferred names:

- Antiplatelet drugs and anticoagulants (except medications listed in Section **Error! Reference source not found.**). (ATC code B01AA-B01AF: B01AA: Vitamin K antagonists, B01AB: Heparin group, B01AC: Platelet aggregation inhibitors excluding heparin, B01AE: Direct thrombin inhibitors, B01AF: Direct factor Xa inhibitors)
- Lipid-lowering agents (ATC code C10: Lipid modifying agents)
- Antihypertensive drugs (ATC codes C02-C09: C02: Antihypertensive drugs, C03: Diuretic drugs, C04: Peripheral vasodilators, C05: Vasoprotective drugs, C07: Beta blocking agents, C08: Calcium channel blockers, C09: Agents acting on the renin-angiotensin system)

Concomitant procedures will be summarized in a table.

7.7 Study Drug Exposure and Compliance

A subject will be considered as treated in a period as long as this subject received any amount of study drug in that period. A treatment period is defined as a period in which the subject received any amount of study drug. A treatment period for a specific drug is defined as a period in which the subject received any amount of that drug.

The exposure to study drug will be summarized including the periods (IV period, Oral period), total number of doses taken, number and percentages of subjects by treatment periods, treatment duration category (i.e. 1-2 weeks, 3-4 weeks..., 10-12 weeks) by cumulatively (number of subjects will be decreased by time).

Dosing data will also be presented in a by-subject listing.

The IV treatment compliance in % = $100 \times (\text{number of completed infusions} / \text{expected number of infusions to be taken})$. If a subject completed the IV treatment period, the expected number of infusions is 14 (received 1 infusion per day for 14 days).

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

Compliance in % = $100 \times (\text{number of tablets dispensed} - \text{number of tablets returned}) / (\text{expected number of tablets to be taken})$

Whereby **expected number of tablets to be taken** = $6 \times (\text{date of last dose} - \text{date of first dose} + 1) - 2 \times (3 - \text{time of last dose}) - 2 \times (\text{time of first dose} - 1)$

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

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

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.

Treatment compliance percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, min, and max). The percentage of patients whose compliance is <80% or >120% will be summarized.

7.8 Efficacy Analysis

The primary and secondary endpoints will be analyzed in randomized subjects who received at least one dose of study drug. Efficacy analysis will use population FAS and PPS.

The percent change from baseline in ICD, the absolute change from baseline in ACD, the percent change from baseline in ACD, the absolute change from baseline in ICD, and change from baseline in SF-36 will be analyzed using a mixed model for repeated measures (MMRM) analysis of covariance with treatment, center, sex, age group, visit, treatment-by-visit interaction as fixed effects, baseline value as covariate, and subject as a random effect. Comparisons between actovegin and placebo will be performed on all assessment points, by reporting LSMeans and the difference in LSMeans along with p-values and 95% confidence intervals. The MMRM analysis will be performed using observed case data, and a missing at random assumption. The effect at each time point for each treatment is allowed to vary freely and an unstructured covariance matrix is assumed. Risk factors (e.g. smoking status and diabetes status, etc) effect on the primary efficacy endpoint will be analyzed by stepwise regression, to determine whether these risk factors should be included in the MMRM model or not.

Proportion of subjects (i.e. patients) having rest pain at 12 and 24 weeks will be analyzed by logistic regression and the odds ratio between Actovegin and Placebo will be determined along with p-value and 95% confidence intervals. The analysis for proportion of subjects having a revascularization procedure at any time during the 24 weeks will be analyzed similarly.

The primary efficacy endpoint and the secondary efficacy endpoints will be analyzed using the PPS for supportive analyses purpose.

7.8.1 Primary Efficacy Endpoint(s)

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

7.8.2 Secondary Efficacy Endpoint(s)

- 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.

7.8.3 Additional Efficacy Endpoint(s)

The following additional efficacy endpoints will be evaluated:

- The absolute change in ICD from Baseline to 2, 12, and 24 weeks after randomization.
- The percent change in ACD from Baseline to 2, 12, and 24 weeks after randomization.
- Subgroup analysis for the efficacy endpoints (percent (or absolute) change in ICD (or ACD) from Baseline to 2, 12, and 24 weeks after randomization) will be performed by following for the exploratory analysis purpose:
 - Age group (<65 or ≥65 years of old)
 - Diabetic and non-diabetic patients
 - Patients with aorto-iliac or femoro-popliteal lesions
 - Current smokers, former smokers, and never-smokers
- Following efficacy endpoints will be presented by figures: Percent change from baseline in ICD (or ACD) by time (BL, Week 2, Week 12, Week 24) – FAS; Absolute change from baseline in ICD (or ACD) by time (BL, Week 2, Week 12, Week 24) - FAS.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

7.9.1 Pharmacokinetic Analysis

Not applicable.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

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.

7.11.1 Adverse Events

The definition of treatment-emergent AEs (TEAE) is defined as any AE that occurs after administration of the first dose of any study treatment through 30 days after the last dose of any study treatment.

AEs will be coded using MedDRA (Medical Dictionary for Regulatory Activities) version 22.0 or above, and will be summarized by system organ class and preferred term in the treatment period (TEAEs) and in the entire study. Study period is from Day 1 (first dose date) to the end of 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. For Tables by SOC/PT, SOC is sorted using alphabetical order and PTs are sorted in decreasing frequency based on the total number of subjects.

All AEs (include the verbatim terms) will be presented in a by-subject listing.

Summary tabulations will include the following categories:

- Overview of Treatment-Emergent Adverse Events
- Overview of Adverse Events during Study Period
- Overview of Adverse Events by Study Period
- Treatment-Emergent AEs by System Organ Class and Preferred Term
- AEs by System Organ Class and Preferred Term during Study Period
- Pre-treatment AEs by System Organ Class and Preferred Term
- TEAEs by System Organ Class and Preferred Term During IV Treatment Period
- TEAEs by System Organ Class and Preferred Term During Oral Treatment Period
- AEs by System Organ Class and Preferred Term During Follow-Up Period
- TEAEs by System Organ Class and Preferred Term by Events
- Drug-Related Treatment-Emergent AEs by System Organ Class and Preferred Term
- Intensity of Treatment-Emergent AEs by System Organ Class and Preferred Term
- Intensity of Drug-Related Treatment-Emergent AEs by System Organ Class and Preferred Term

- The Most Commonly Reported Treatment-Emergent AEs by Preferred Term (i.e., those events reported by $\geq 1\%$ of all subjects)
- Serious Treatment-Emergent AEs by System Organ Class and Preferred Term
- Serious AEs by System Organ Class and Preferred Term during Study Period
- Treatment-Emergent AEs Leading to Study Drug Discontinuation by System Organ Class and Preferred Term
- Listing of Deaths

Most commonly reported ($\geq 1\%$ of all subjects in each group) treatment-emergent AEs will be presented by preferred term only. Subjects with the same AE more than once will have that event counted only once within each preferred term.

An overall summary AE table will include numbers and percentages of subjects who had any AE, AE by relationship (drug-related, not related), AE by severity (mild, moderate, and severe), serious AE (SAE), drug-related SAE, not related SAE, AE leading to study drug discontinuation, and on-study deaths.

In addition, a by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs regardless of treatment-emergent AE status).

A by-subject listing of AEs leading to deaths occurring on-study will be presented.

A by-subject listing of treatment-emergent AEs leading to discontinuation of any study drug will be presented. All AEs resulting in discontinuation of any study drug occurring on-study will be displayed.

7.11.2 Clinical Laboratory Evaluations

Absolute values and changes from baseline in clinical safety laboratory tests will be summarized for each treatment group using descriptive techniques. Values outside normal ranges, potentially clinically significant values, and the markedly abnormal values (MAV) will be flagged and tabulated.

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units.

If a subject has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will also be presented. Unscheduled laboratory test results will not be included in the tables by visit, but they will be listed in the listing. The parameters to be analyzed are as follows:

- **Hematology:** hemoglobin, hematocrit, erythrocytes, thrombocytes, leukocytes and white blood cell count.
- **Serum chemistry:** creatinine, total bilirubin, albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, Gamma glutamyl transferase (GGT), Creatine kinase, sodium, potassium, Cholesterol (total, high-density lipoprotein, and low-density lipoprotein), and Triglycerides.

The number and frequency of the potentially clinically significant values (PCS) for above Laboratory tests will be summarized by visit for following categories: Normal, Abnormal but not clinically significant, and Abnormal and clinically significant.

Shift tables will be constructed for laboratory parameters to tabulate changes by values of Low, Normal, High based on the local Lab normal ranges for scheduled visits, or criteria for markedly abnormal values (MAV) from baseline to post baseline worst value (includes unscheduled visit records) (see Takeda Guidance for Defining Markedly Abnormal Values Used in Statistical Analyses, TOOL-001387 (1.0), 02JUN2016). Parameters to be tabulated will include:

- **Hematology:** hemoglobin, thrombocytes
- **Serum chemistry:** ALT, AST, ALP, creatinine, total bilirubin.

Mean laboratory values and box plots over time for key lab parameters will be produced, including but not limited to the liver function tests (ALT, AST, alkaline phosphatase, and total bilirubin).

By-subject listings to be presented include results from the clinical laboratory tests for hematology, serum chemistry, and urinalysis.

7.11.3 Vital Signs

Absolute values and changes from baseline in vital signs and weight will be summarized for each treatment group using descriptive techniques. Values outside the criteria for markedly abnormal values will be flagged and tabulated (see Takeda Guidance for Defining Markedly Abnormal Values Used in Statistical Analyses, TOOL-001387 (1.0), 02JUN2016).

The actual values of vital sign parameters including blood pressure, heart rate, and body weight, will be summarized over time for each treatment arm. Change from baseline will also be presented.

A by-subject listing will also be presented.

7.11.4 12-Lead ECGs

An overall summary ECG table will include numbers and percentages of subjects who had ECG result of Normal, NCS, CS from CRF ECG page by treatment group. A by-subject listing of ECG result will also be presented.

7.11.5 Other Observations Related to Safety

Physical examination findings will be presented by a listing.

7.12 Interim Analysis

No interim analysis is planned.

7.13 Changes in the Statistical Analysis Plan

{None}

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9.0 APPENDIX

Appendix A Schedule of Study Procedures

Day	Screening Period	Treatment Period							Follow- up Period		
		Randomization (Baseline)	Infusion Treatment (IV)			Oral Treatment					
	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 exercise habits	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)

Day	Screening Period	Treatment Period									
		Randomization (Baseline)	Infusion Treatment (IV)			Oral Treatment			Follow- up Period		
	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 1, AEs should be checked before (since last visit) 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.

(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 and ≤ 2 weeks.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	13-Nov-2019 15:36 UTC

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