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LLG783

Clinical Trial Protocol CLLG783X2201

A Patient and Investigator-blinded, randomized, placebo-controlled study of LLG783 in patients with peripheral artery disease (PAD) and intermittent claudication

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the SOM for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO& PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead for this study
- The fax number(s) and email address(es) are located in the SOM.

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List of abbreviations

6MWT	six-minute walk test
ABI	Ankle-brachial index
ADA	Anti-drug antibody(ies)
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CFR	U.S. Code of Federal Regulation
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
CNS	central nervous system
CO_2	carbon dioxide
CRF	case report form
CRO	Contract Research Organization
CV	coefficient of variation
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay

FDA	Food and Drug Administration
FIH	First in Human
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HEK	human embryonic kidney (cells)
HIV	human immunodeficiency virus
IA	interim analysis
IB	Investigator's brochure
IC	informed consent
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	immunogenicity
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
i.v.	intravenous
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LOCF	last observation carried forward

MedDRA	Medical dictionary for regulatory activities
MDRD	modification of diet in renal disease
mg	milligram(s)
mL	milliliter(s)
MRSD	maximum recommended starting dose
MWD	maximum walking distance
NADPH	nicotinamide adenine dinucleotide phosphate
NIRS	near-infrared spectroscopy
NOAEL	no observable adverse effect level

PAD	peripheral artery disease
PD	pharmacodynamics(s)

PK	pharmacokinetic(s)
PRO	patient reported outcome
PT	prothrombin time
QoL	quality of life
RBC	red blood cell(s)
ROS	reactive oxygen species
s.c.	subcutaneous
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SAE	serious adverse event
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SOM	Site Operations Manual
TMDD	target mediated drug disposition
ULN	upper limit of normal
WBC	white blood cell(s)
WOCBP	Women of child-bearing potential
WOCF	worst observation carried forward

Pharmacokinetic definitions and symbols

AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
CL	The systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration [volume / time]
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Cmin,ss	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
MRT	Mean residence time determined as AUMCinf/AUCinf following intravenous administration [time]
T1/2	The terminal elimination half-life [time]
Tmax	The time to reach the maximum concentration after drug administration [time]
VL	Volume of distribution
Vss	The volume of distribution at steady state following intravenous administration [volume]
Vz/F	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of patients fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Patient	An individual with the condition of interest
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Screen Failure	A patient who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)

Subject number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CLLG783X2201
Full Title	A Patient and Investigator-blinded, randomized, placebo-controlled study of LLG783 in patients with peripheral artery disease (PAD) and intermittent claudication
Brief title	Study of pharmacodynamics, pharmacokinetics, safety and tolerability of LLG783 in patients with peripheral artery disease (PAD) and intermittent claudication
Sponsor and Clinical Trial Phase	Novartis Phase IIa
Intervention type	Biologic
Study type	Interventional
Purpose and rationale	This study is designed to determine whether LLG783 displays the clinical safety and efficacy profile, after multiple i.v. doses, to support further development in patients with PAD and intermittent claudication.
Primary Objective(s)	• To evaluate the safety and tolerability of LLG783 in patients with PAD and intermittent claudication after 16 weeks of exposure to LLG783. • To evaluate the effect of LLG783 on functional capacity after 3 months of treatment in patients with PAD and intermittent claudication.
Secondary Objectives	• To investigate the PK of LLG783 in patients with PAD and intermittent claudication. • To evaluate the effect of LLG783 on symptomatic functional capacity after 3 months of treatment in patients with PAD and intermittent claudication.
Study design	This is a non-confirmatory, randomized, patient and investigator-blinded, placebo-controlled, parallel-group study
Population	Approximately 40 male and female patients, ages 40-85 years of age (inclusive) with clinical evidence of PAD and intermittent claudication will be enrolled into this study. **Corporate Confidential Information**
Key Inclusion criteria	• Clinical evidence of PAD and intermittent claudication. Intermittent claudication, as defined by pain with exertion in either leg • On stable medical therapy for PAD and PAD symptoms, which may include statins, aspirin, and anti-platelet medications (as medically indicated) unless individually contraindicated, for at least 4 weeks prior to the screening visit. • Vital signs must be within the following ranges: o body temperature between 35.0-37.5°C o systolic blood pressure, 90-159 mm Hg o diastolic blood pressure, 50-99 mm Hg

	○ pulse rate, 50 - 90 bpm • Moderately impaired ambulatory function judged by the investigator to be due primarily to PAD and assessed by a maximum walk distance between 50 and 400 meters (inclusive of these values) at the screening 6MWT.
Key Exclusion criteria	• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. • Patients who meet any of the following PAD related criteria: ○ Patients actively attending and participating in a supervised exercise rehabilitation program (patients who have already completed such a program and remain symptomatic may be included). ○ Patients with any condition other than PAD that limits walking ability. ○ Known inflammatory disease of the arteries (other than atherosclerosis; e.g. Thromboangiitis obliterans). ○ Clinical evidence of critical limb ischemia including new or non-healing ulcers (felt secondary to critical limb ischemia), new or recent onset of resting pain in the lower extremities particularly at night (felt secondary to critical limb ischemia) and/or gangrene of the lower extremities (Fontaine stage III-IV) . • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 150 days after stopping of investigational drug. • Any of the following concomitant cardiovascular or metabolic conditions or diseases: ○ Myocardial infarction within 6 months of screening. ○ Stroke within 6 months of screening. ○ History of clinically significant ventricular arrhythmias, according to the discretion of the investigator, within 6 months of screening. ○ Significant ECG abnormalities, according to the discretion of the investigator, at screening. ○ History of sustained and clinically significant supraventricular arrhythmias (e. g. associated with hemodynamic compromise) within 6 months of screening. ○ Chronic heart failure New York Heart Association Class III or IV. ○ Known presence of aortic aneurysm > 5 cm. ○ Uncontrolled diabetes as defined by a random fasting glucose level of 13 mmol/L or 240 mg/dL or a HbA1c greater than 9% as measured at screening. Diabetes should be treated as appropriate during the study.
Study treatment	• LLG783 • Placebo
Pharmacokinetic assessments	• AUCinf, AUClast, AUC0-t, AUC0tau, Cmax and Tmax
Efficacy/PD assessments	• Maximum walking distance assessed by 6-minute walk test (6MWT) • Pain-free walking distance assessed by 6MWT

Key safety assessments	• Monitoring of AEs, including observations made during physical examinations • Vital signs • Laboratory evaluations (blood and urine) • ECGs
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Data analysis	• All safety and tolerability data (including AEs, vital signs, laboratory evaluations, and ECGs) will be listed by subject and summarized by treatment. • The change from baseline in maximum walking distance (MWD) will be analyzed in a repeated measures mixed effects model with treatment, day, and the treatment-by-day interaction as fixed effects and baseline MWD as a covariate. The least-square mean change from baseline in MWD for each day will be estimated from the model for each treatment along with the treatment difference and the associated p-value and two-sided 80% confidence interval.
Key words	Peripheral artery disease, PAD, intermittent claudication, claudication, 6-minute walk test, **Corporate Confidential Information** peripheral vascular disease

1 Introduction

1.1 Background

Intermittent claudication is a common complication in peripheral artery disease (PAD) patients, affecting ~10 million people in the United States and over 150 million people worldwide (Fowkes et al 2017). As a result of lower extremity skeletal muscle ischemia, patients suffer from muscle fatigue and pain on exertion, which limits mobility and reduces quality of life (QoL). Current drug therapy has limited efficacy, and surgical revascularization is not an option for many patients (Go et al 2014; Hirsch and Duval 2013).

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure (IB).

1.4 Study purpose

This study is designed to determine whether LLG783 displays the clinical safety and efficacy profile, after multiple i.v. doses, to support further development in patients with PAD and intermittent claudication.

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objective(s)***

• To evaluate the safety and tolerability of LLG783 in patients with PAD and intermittent claudication after 16 weeks of exposure to LLG783.	• AEs (including observations made during physical examinations as appropriate)
	  • Incidence
	  • Severity
	• Vital signs including:
	  • Pulse rate
	  • Blood pressure (BP)
	  • Respiratory rate
	  • Body temperature
	• Laboratory evaluations
	  • Hematology
	  • Clinical chemistry
	  • Urinalysis
	• Electrocardiogram (ECG) intervals

• To evaluate the effect of LLG783 on functional capacity after 3 months of treatment in patients with PAD and intermittent claudication.	• Maximum walking distance assessed by 6-minute walk test (6MWT)

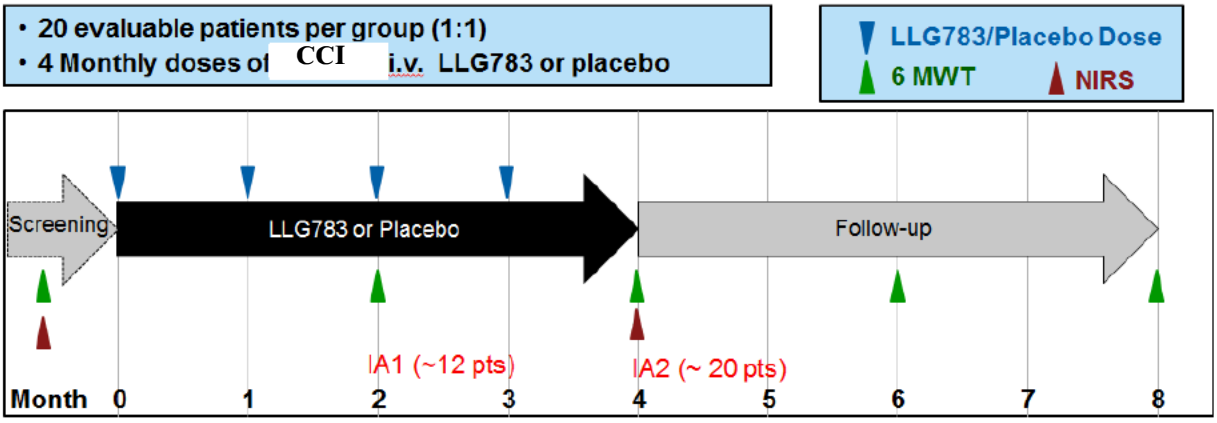
2.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To investigate the PK of LLG783 in patients with PAD and intermittent claudication.	• PK parameters will be determined, including: AUCinf, AUClast, AUC0-t, AUC0tau, Cmax and Tmax
• To evaluate the effect of LLG783 on symptomatic functional capacity after 3 months of treatment in patients with PAD and intermittent claudication.	• Pain-free walking distance assessed by 6MWT

3 Investigational plan

3.1 Study design

Figure 3-1 Study Design



This is a non-confirmatory, randomized, patient and investigator-blinded, placebo-controlled, parallel-group study in patients with PAD and intermittent claudication. Approximately 40 randomized patients will be treated in a 1:1 ratio to receive LLG783 or placebo as an i.v. infusion of CCI i.v. dosing once every 4 weeks for a total of 4 doses over a period of 12 weeks/3 months. Key study assessments are conducted at week 16 (month 4) of the study (i.e. after 16 weeks of exposure), which is one month after the final dose of study medication.

The dose may be altered based on review of data from the 1st interim analysis (IA).

Potential study participants will undergo screening assessments, including 6MWT and ABI, to determine eligibility. Patients who pass the screening evaluations will come to the investigational site on Day 1, at which time inclusion and exclusion criteria will be re-reviewed, and eligible patients will be randomized and dosing will commence.

Assessments of functional capacity (6MWT) will be made at weeks 8 and 16 (days 57 and 113) following the first dose of study medication, with follow-up functional assessments at weeks 24 and 32 (days 169 and 225) following the first dose of study medication (i.e. 2 and 4 months following the last dose of medication, see Figure 3-1). These follow-up assessments will be performed to help define durability of clinical response as LLG783 exposure declines. The primary endpoint of improved walk distance will be adjudicated based on the 8 and 16 week data points, though the 24 and 32 week data may be used in final statistical modeling.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), as well as AE and SAE monitoring.

Patients who discontinue the study for reasons other than safety prior to the week 16 visit may be replaced in order to ensure ability to assess 40 patients with a functional assessment after 16 weeks of exposure.

3.7 Risks and benefits

There is no benefit expected for patients participating in this study.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria, and close clinical monitoring.

Because patients will all receive standard-of-care for PAD, there will be no disadvantage to those receiving placebo over active drug.

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PAD patients will be monitored for any effects on standard hematologic, coagulation, renal, liver and other chemistries routinely measured to detect changes in homeostasis. However, there may be unknown risks of LLG783 in PAD patients which may be serious.

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Though there is no reason to believe that patients with PAD will be at increased risk of adverse outcomes in the development of ADAs, patients will be carefully monitored for development of such ADA or ADA-related reactions during the study.

As LLG783 is a monoclonal antibody, no specific drug-drug interactions are anticipated.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in Section 4.2 (Exclusion Criteria). If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

For those patients participating in the lower extremity assessment of microvascular blood flow and skeletal muscle perfusion, there is minimal risk associated with the NIRS procedure. Specifically, discomfort from inflation from the blood pressure cuff during the NIRS assessment protocol may occur. Discomfort would be anticipated to be transient and resolve following deflation of the cuff.

3.7.1 Blood sample volumes

A maximum of 500 mL of blood is planned to be collected over a period of approximately 35 weeks, from each patient as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment Schedule (Section 8.1).

A summary blood log is provided in the SOM. Instructions for sample collection, processing, storage and shipment information is available in the Central Laboratory Manual.

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4 Population

Approximately 40 patients with PAD and intermittent claudication will be randomized into the study to be treated with 4 i.v. doses of study medication vs. placebo.

Replacement patients will be enrolled to replace those patients who discontinue the study for reasons other than safety before their 16-week 6MWT visit. This includes patients who, for clinical reasons, require an interventional procedure (e.g. angioplasty, stenting, or bypass surgery) after randomization, but before the 16 week (day 113) visit.

The Investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible patients.

Patient selection is to be established by checking through all eligibility criteria at screening.

This criteria should be re-reviewed at the time of their Day 1 visit prior to the administration of the first dose. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a patient from enrollment into the study.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent (IC) must be obtained before any study assessment is performed.
2. Male and female patients 40 to 85 years of age (inclusive) at screening with clinical evidence of PAD and intermittent claudication (Fontaine stage II) (Hardman et al 2014).
   Intermittent claudication, as defined by pain with exertion in either leg (this may include atypical symptoms, e.g. fatigue, paresthesias, pallor, etc.) **AND** any **one** of the following:
   a. resting ABI of 0.40-0.90 (inclusive) in at least one leg;
   b. **OR** for patients with a resting ABI >0.90 but ≤ 1.0, a decrease in ABI of ≥20% with exercise (to be measured immediately following completion of 6MWT at screening) in at least one leg;
   c. **OR** a decrease in ankle pressure ≥30 mmHg with exercise in at least one leg;
   d. **OR** for patients with an ABI >0.90, an abnormal toe-brachial index (TBI) <0.70.

   Note: documented values within 3 months of signing the informed consent are acceptable provided that there has been no peripheral revascularization in the interim.
3. On stable medical therapy for PAD and PAD symptoms, which may include statins, aspirin, and anti-platelet medications (as medically indicated) unless individually contraindicated, for at least 4 weeks prior to the screening visit.
4. Vital signs must be within the following ranges:
   a. body temperature between 35.0-37.5°C
   b. systolic blood pressure, 90-159 mm Hg
   c. diastolic blood pressure, 50-99 mm Hg
   d. pulse rate, 50 - 90 bpm

   Refer to the SOM for guidance on collecting vital signs and repeated vital sign assessments in case screening vital signs are out-of-range.
5. Moderately impaired ambulatory function judged by the investigator to be due primarily to PAD and assessed by a maximum walk distance between 50 and 400 meters (inclusive of these values) at the screening 6MWT.

6. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Participation in any clinical investigation within four (4) weeks prior to enrollment or use of other investigational drugs at the time of enrollment, or within 5 half-lives at the time of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations. Patients previously enrolled in clinical trials of stem cell therapy for PAD may be included if this therapy ended at least 6 months prior to enrollment.
2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
3. Patients who meet any of the following PAD related criteria:
   a. Patients actively attending and participating in a supervised exercise rehabilitation program (patients who have already completed such a program and remain symptomatic may be included).
   b. Patients with any condition other than PAD that limits walking ability.
   c. Known inflammatory disease of the arteries (other than atherosclerosis; e.g. Thromboangiitis obliterans).
   d. Clinical evidence of critical limb ischemia including new or non-healing ulcers (felt secondary to critical limb ischemia), new or recent onset of resting pain in the lower extremities particularly at night (felt secondary to critical limb ischemia) and/or gangrene of the lower extremities (Fontaine stage III-IV) .
4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 150 days after stopping of investigational drug.

   Highly effective contraception methods include:

   - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the patient, and only in countries that accept "total abstinence" as effective contraception). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment (e.g. FSH).
   - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.

- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, women should be stable on the same pill for ≥ 3 months before taking investigational drug.

If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation ≥ 6 weeks prior to the screening visit. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5. Any of the following concomitant cardiovascular or metabolic conditions or diseases:
   a. Myocardial infarction within 6 months of screening.
   b. Stroke within 6 months of screening.
   c. History of clinically significant ventricular arrhythmias, according to the discretion of the investigator, within 6 months of screening.
   d. Significant ECG abnormalities, according to the discretion of the investigator, at screening.
   e. History of sustained and clinically significant supraventricular arrhythmias (e. g. associated with hemodynamic compromise) within 6 months of screening.
   f. Chronic heart failure New York Heart Association Class III or IV.
   g. Known presence of aortic aneurysm > 5 cm.
   h. Uncontrolled diabetes as defined by a random fasting glucose level of 13 mmol/L or 240 mg/dL or a HbA1c greater than 9% as measured at screening. Diabetes should be treated as appropriate during the study.
6. Any of the following concomitant hepatic or renal conditions or diseases:
   a. Patients with severe renal impairment defined as eGFR < **15** mL/min/1.73m2 [as calculated by the MDRD (Modification of Diet in Renal Disease) method] or those receiving current or planned dialysis or ultrafiltration.
   b. Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C - including positive hepatitis B surface antigen or hepatitis C test), or alanine aminotransferase/aspartate aminotransferase (ALT/AST) levels > 2.5 times upper limits of normal (ULN) or total bilirubin > 2 times ULN at screening.
7. History of any of the following chronic conditions:
   a. Malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin), treated or untreated, within the past **3 years**, regardless of whether there is evidence of local recurrence or metastases.
   b. Hemoglobin levels < 10.6 g/dL at screening.

c. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
d. History of any hypercoagulable or bleeding disorders.

8. Major surgical procedure (such as coronary artery bypass grafting, carotid endarterectomy, abdominal surgery) ≤ 6 months before screening (≤ 4 weeks before screening for coronary stent placement or angioplasty) or planned coronary revascularization or any other major surgical procedure planned to occur during the planned time frame of the study. Patients who have undergone peripheral vascular interventions > 6 months prior to screening may still be considered eligible, provided they meet all other inclusion/exclusion criteria. Patients with actively planned/scheduled lower extremity peripheral vascular interventions within the first 4 months after enrollment should not be enrolled. However, if clinically indicated during the study, a patient may undergo peripheral vascular intervention.
9. Any surgical or medical condition that in the opinion of the Investigator may place the patient at higher risk from his/her participation in the study.
10. History of significant and active drug or alcohol abuse that could interfere with conduct of the trial within the 12 months prior to dosing. Note: Investigator may establish veracity of patient history with drug or alcohol testing as deemed necessary.
11. History of multiple and clinically significant recurring drug allergies.
12. History of allergy to the investigational compound / compound class (e.g. allergic reactions to other protein therapeutics) being used in this study.
13. History of any transplant with the exception of skin or cornea.
14. Patients unable to hold all narcotic pain relievers for 24 hours prior to performance of the 6MWT. (Instructions to this effect will be provided to enrolled patients).
15. Patients who are taking any other monoclonal antibody at screening are not necessarily excluded from the study, but the site MUST contact the Novartis study safety monitor so that the monoclonal antibody information can be reviewed before confirming whether or not the patient can be enrolled.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Refer to Section 8.3 (Patient Screening) for information regarding re-screening.

5 Restrictions for Study Subjects

Patients should be informed and reminded of the restrictions outlined in this section at each visit for the duration of the study.

5.1 Contraception requirements

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement outlined in Section 4.2 (Exclusion Criteria).

If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

Women who become pregnant during the study should NOT be administered any further doses of study drug. Refer to Section 9.6 for Pregnancy Reporting requirements.

5.2 Prohibited treatment

Use of the treatments displayed in Table 5-1 is NOT allowed throughout the prohibited period noted in the table.

Table 5-1 Prohibited medication

Medication	Prohibited period	Action to be taken
Monoclonal antibody use must be reported to the Novartis study safety monitor to be reviewed before a patient can be enrolled or continued in this study.	Within 6 months of screening through to the end of the study	Novartis safety monitor may exclude patient from study or require discontinuation of study treatment in cases where highly similar classes/types of antibodies are prescribed (and replacement of patient in study)
Change in type or dosage of narcotic pain relievers; OR Change in type or dosage of PAD specific symptom-relief drugs (specifically: cilostazol, pentoxifylline, or naftidrofuryl)	4 weeks prior to screening through week 16	Notify Novartis study team as it may be determined that it is necessary to discontinue study treatment and replace the patient

5.3 Dietary restrictions and smoking

Not applicable.

Smoking and alcohol history will be collected and documented in the CRF at screening.

5.4 Other restrictions

Not applicable.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Pharmacy Manual.

6.1.2 Additional study treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

6.2 Treatment arms

Patients will be assigned to one of the following 2 treatment arms in a ratio of 1:1:

- LLG783 (**CCI**)
- Placebo (0 mg/vial)

6.3 Treatment assignment and randomization

At the randomization visit, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or delegate will contact the IRT after confirming that the patient fulfills all the eligibility criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment- arm. The randomization number will not be communicated to the caller.

The randomization number is only used to identify which treatment the patients have been randomized to receive. The Subject number assigned to a patient at screening remains the unique identifier for the patient throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A patient randomization list will be produced by the IRT provider, or by a delegate under their supervision, using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

The randomization scheme for patients will be reviewed and approved by a member of the Novartis Randomization Office.

Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of patients.

6.4 Treatment blinding

Table 6-2 Blinding and un-blinding plan

	Time or Event			
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**	**IA & dose escalation**
Subjects	B	B	UI	B
Site staff e.g. investigator and study nurse	B	B	UI	B
Unblinded site staff *(*)* e.g. pharmacy staff	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff *(**)* e.g. for drug re-supply, unblinded monitor, sample analytics	B	UI	UI	UI
Statistician/statistical programmer/biomarker expert	B	B	UI	UI
Independent committees (e.g. DMC) used for assessing interim results	NA	NA	NA	NA
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	B	B	UI	UI

IA Interim analyses

UI Allowed to be unblinded on individual patient level

B Remains blinded

At Database lock all roles can be unblinded

This is a patient and investigator-blinded study: patients and investigator will remain blinded to study treatment throughout the study (except in the case of a safety event necessitating unblinding). The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

With the exception of unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment during treatment allocation and at the point of subject dosing but may be unblinded to the treatment assignment of an individual subject in case of a safety event necessitating unblinding.

Unblinding a single subject for safety reasons (necessary for subject management) will occur via an emergency system in place at the site.

*** Unblinded site staff:** Drug product will be supplied in bulk, so an unblinded pharmacist, or appropriately designated study site staff, who is independent of the study team will be required in order to maintain the blind. This unblinded associate at the site will be notified by the IRT system that a patient is randomized and to which treatment arm, which will then enable them to prepare the study drug.

**** Unblinded sponsor staff:** The following unblinded sponsor roles are required for this study:

Unblinded monitor

Unblinded sample analyst(s) (for example, PK, biomarker, and IG blood)

The unblinded monitor is required to review drug accountability and allocation at site. The unblinded monitor is not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual subjects.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office) to facilitate analysis of the samples. The sample analysts will provide the sample data to the team under blinded conditions. Both the pharmacist and bioanalyst will keep this information confidential until clinical database lock.

The study statistician will be able to access the randomization list for IAs and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in the blinding table above. For example, unblinded summaries and unblinded individual data can be shared with the team for planned and unplanned IAs.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert) are allowed to access treatment assignment information for the purpose of conducting planned and unplanned IAs.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project while the study is ongoing.

Following final database lock all roles may be considered un-blinded.

6.5 Treating the patient

LLG783 will be administered via i.v. **Corporate Confidential Information**

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

Refer to the Pharmacy Manual for does preparation and administration instructions.

6.6 Permitted dose adjustments and interruptions of study treatment

Planned study drug dose adjustments and/or interruptions are not permitted for this study.

In the case of a suspected serious infusion reaction, the infusion must be stopped and the sponsor notified.

Short interruptions of the i.v. infusion may be tolerated, for example, to re-insert a cannula for i.v. drug administration.

Any changes must be recorded on the Dosage Administration Record case report form (CRF).

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must occur only when it is required to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis study monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to IRT in case of an emergency. The investigator will need to provide:

- protocol number

- study drug name (if available)
- subject number

In addition, the investigator must provide oral and written information to inform the patient how to contact the investigator's backup in case of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency un-blinding to assess whether or not study treatment should be discontinued for a given patient.

6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with LLG783, as detailed in Section 8.7.

All study treatment will be administered at the clinical center, by qualified site staff, under the supervision of the investigator or qualified designee.

All study treatment dispensed must be recorded in the Drug Accountability Log.

6.9 Recommended treatment of AEs

The investigator and site staff must carefully observe the patients for any AE. In principle, any AE should be treated according to clinical practice.

Specific AEs, which can occur following i.v. or s.c. administration of monoclonal antibodies such as LLG783, are hypersensitivity reactions. The clinical symptoms of hypersensitivity reactions can be very variable. Typical manifestations are itching, flushing, headache, nausea/vomiting, hypotension, urticaria, bronchospasm, or angioedema. In the event of a hypersensitivity reaction, the infusion has to be stopped, if it is ongoing. Next, assessment and treatment should be done for anaphylaxis/ anaphylactoid reaction if indicated, and supportive care be initiated. Fluids, vasopressors, corticosteroids, antihistamines, bronchodilators, epinephrine and oxygen should be on hand. Specifically, in the case of an SAE suggestive of anaphylaxis or anaphylactoid reaction, acute cytokine release syndrome, or vasculitis-like reaction, the investigator should strongly consider prompt administration of epinephrine, corticosteroids, antihistamines, and/or plasmapheresis as therapeutic options. Treatment with plasmapheresis may be helpful in situations in which decreasing the systemic concentration of LLG783 may be of clinical benefit, based on the capacity of plasmapheresis to remove IgG antibody, such as the IgG monoclonal antibody LLG783, from the intra-and extra-vascular compartments.

If any other signs and symptoms of potential immune-related reactions are detected, appropriate intervention should be instituted, including full supportive care and consideration of discontinuation of further LLG783 treatment, which may mitigate more serious reactions.

For further details see Risk / Benefit section of the IB.

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.10 Rescue medication

There is currently no specific recommendation for rescue medication for this compound, but standard-of-care medications for AEs should be administered at PI discretion. See Section 6.9 for recommended treatment of AEs.

If clinically indicated during the study, a patient may undergo peripheral vascular intervention for treatment of their underlying PAD (see details for exclusion criteria related to interventions in Section 4.2).

Use of concomitant medication or therapy must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.11 Concomitant treatment

In principle, it is allowed that all patients participating in the study can continue their regular medication, unless the concomitant medication is not allowed per exclusion criteria as described in the prohibited treatment section. Medication intake should occur at the same time throughout the study; morning medication should be taken early enough so that it does not interfere with the dosing on dosing days. Accordingly, the regular intake time should be adapted if needed.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

The investigator must instruct the patient to notify the study site about any new medications he/she takes after being enrolled into the study.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a patient or, if the patient is already enrolled, to determine if the patient should continue participation in the study.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last patient completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision.

All patients who receive at least one dose of study medication should have a safety follow-up phone call conducted approximately 140 days after last administration of study treatment IF they fail to return to the site for scheduled site visits prior to 140 days following the administration their last dose. The information collected from the follow-up phone call will be kept as source documentation.

All SAEs reported during this time period must be reported as described in Section 9.2 and the SOM. Documentation of attempts to contact the patient should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time.

The investigator should discontinue study treatment for a given patient if, on balance, they believe that continuation would be detrimental to the patient's well-being.

Study treatment MUST BE discontinued for a given patient under the following circumstances:

- Patient withdraws consent
- Pregnancy
- Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension. Immediate interruption of the infusion to administer study treatment is required in such cases if the reaction occurs during infusion.
- Circumstances where the Sponsor or investigator determine that continuation of treatment puts the patient's safety at significant risk.

There may also be situations where the patient's safety is not considered to be at risk, but where study treatment may be temporarily suspended at the discretion of the investigator, such as:

- A protocol deviation (missed assessment, use of prohibited medication)
- Lab value for individual patient is outside the normal range

Under these circumstances, the Investigator may choose to hold study drug pending further investigation and collection of additional data, or discussion with the Sponsor. If after such deliberation, the Investigator deems the study drug safe to be restarted at a time point which is outside the treatment window for that dose, the patient should skip the interrupted dose and restart dosing at the next dose (unless this is the final dose, in which case, no further doses should be given). This missed dose should be reported in the CRF by the investigator. No replacement dose should be given (i.e. there should be no dosing beyond the scheduled month dosing window) to avoid exposure longer than that study in the 13-week GLP toxicology study.

All visits, including dosing visits, should be scheduled as per the study assessment table (see the SOM for visit windows).

In case of an unavoidable delay in dosing visits, the site may still dose a patient if the visit is ≤ 7 days later than the scheduled timepoint. Dosing visits which exceed a 7-day delay should be considered as missed doses. All other scheduled assessments should still take place as per the protocol assessment table for that visit, despite the duration of the delay.

The subsequent visit should, as much as possible, continue to be scheduled as per the original planned visit schedule (i.e. the subsequent visit should NOT be delayed by the same number of days as the delayed dosing visit).

The exception to this request is for the fourth dose. If the fourth (final) dose is delayed, then the week 16 visit should also be delayed by approximately the same number of days to ensure approximately one month between final dose and the week 16 assessments.

Patients who miss more than 1 dose should be discontinued from the study, but should continue to return for safety assessments.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

If discontinuation of study treatment occurs, the investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

Patients who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3, Withdraw of Informed Consent). Where possible, they should return for the assessments indicated by an asterisk (*) in the Assessment Schedule.

If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in Section 7.4 (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore and
- Does not want any further visits or assessments and
- Does not want any further study related contacts and
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

7.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study Stopping rules

The study will be paused and safety data will be reviewed if any of the following criteria are met, and no further dosing or enrollment will take place pending a full safety review conducted by the sponsor:

- One or more patients experience an SAE potentially considered study drug-related.
- If two or more patients experience an AE that is similar, of severe grade (including hypersensitivity reactions or injection site reactions) and potentially considered to be study-drug related.
- The sponsor considers that the aggregate number, severity and/or relatedness of AEs justify postponing or discontinuing the study. This assessment will be made based on periodic review of AEs by the investigator and the sponsor.
- The sponsor requests it.

The study may resume following the safety review if it is deemed safe to proceed.

The study may be stopped early by the Sponsor based on results of IAs. For a detailed example, refer to statistical Section 11.8.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, patients must be seen as soon as possible and treated as prematurely discontinued patients. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment Schedule

Patients should be seen for all visits/assessments as outlined in the Assessment Schedule or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications recorded on the CRF.

Unscheduled visits are permitted throughout the study upon request from the investigator or the study participant.

Table 8-1 Assessment Schedule

Epoch	Screening[1]	Treatment																							
Visit Number (internal use)	1	101					102	103	104			104.100	105			105.100	106				107	108	109	110	199
Visit Name	Screening	Treatment																			Follow-Up				EOS
Days	-21 to -2[1]	1					4	15	29			43	57			71	85				95	113	156	169	225 [10, 11]
Time (post-dose)	-	-1h[2]	0h	1h[3]	2h	4h	-	-	0h[2]	1h[3]	4h	-	0h[2]	1h[3]	4h	-	0h[2]	1h[3]	2h	4h	-	-	-	-	-
Informed consent	X																								
Corporate Confidential Information	X																								
Inclusion / Exclusion criteria	S	S																							
Demography	X																								
Smoking and Alcohol history	X																								
Relevant medical history/current medical conditions	As appropriate throughout study																								
Concomitant medications	As appropriate throughout study																								
Body height	X																								X*
Body weight	X	X					X		X			X	X			X	X					X		X	X*
Vital Signs: Temperature, Blood Pressure, Pulse Rate and Respiratory Rate	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X*
Physical examination	S	S					S		S			S	S			S	S					S		S	S*
ECG evaluation	X	X					X		X			X	X			X	X					X		X	X*

Epoch	Screening[1]	Treatment																						
Visit Number (internal use)	1	101					102	103	104			104.100	105			105.100	106				107	108	109	110	199
Visit Name	Screening	Treatment																			Follow-Up				EOS
Days	-21 to -2[1]	1					4	15	29			43	57			71	85				95	113	156	169	225 [10, 11]
Time (post-dose)	-	-1h[2]	0h	1h[3]	2h	4h	-	-	0h[2]	1h[3]	4h	-	0h[2]	1h[3]	4h	-	0h[2]	1h[3]	2h	4h	-	-	-	-	-
Randomization		X[4]																							
Study drug administration			X						X				X				X								
Pregnancy test	X[5]	X[6]							X[6]				X[6]				X[6]								X*
Hepatitis and HIV screen	S																								
Standard Safety Labs (hematology, chemistry, urinalysis)	X	X					X		X			X	X			X	X					X		X	X*
Fasting Serum Lipid Panel	X																					X			X*
Corporate Confidential Information	X	X					X		X				X				X					X		X	X*
PK blood collection		X		X	X	X	X	X	X			X	X			X	X	X	X	X	X	X	X	X	X*
		X							X			X	X			X	X					X	X	X	X*
Corporate Confidential Information		X		X	X	X	X	X	X			X	X			X	X	X	X	X	X	X	X	X	X*
		X							X				X				X					X			X
		X							X				X				X					X			X
		X											X									X			

Epoch	Screening[1]	Treatment																						
Visit Number (internal use)	1	101					102	103	104			104.100	105			105.100	106				107	108	109	110	199
Visit Name	Screening	Treatment																			Follow-Up				EOS
Days	-21 to -2[1]	1					4	15	29			43	57			71	85				95	113	156	169	225 [10, 11]
Time (post-dose)	-	-1h[2]	0h	1h[3]	2h	4h	-	-	0h[2]	1h[3]	4h	-	0h[2]	1h[3]	4h	-	0h[2]	1h[3]	2h	4h	-	-	-	-	-
Markers																									
		X											X									X			
		X											X									X			
Corporate Confidential Information		X											X									X			
		X																							
	X								X				X				X					X		X	X
	X								X				X				X					X		X	X
6-Minute Walk Test	X												X									X		X	X
	X												X									X		X	X
Corporate Confidential Information	X																					X			
	Once assigned, the device should be worn throughout the study; see SOM for details																								
	X																					X			

Epoch	Screening[1]	Treatment																								
Visit Number (internal use)	1	101					102	103	104			104.100	105			105.100	106				107	108	109	110	199	
Visit Name	Screening	Treatment																			Follow-Up				EOS	
Days	-21 to -2[1]	1					4	15	29			43	57			71	85				95	113	156	169	225 [10, 11]	
Time (post-dose)	-	-1h[2]	0h	1h[3]	2h	4h	-	-	0h[2]	1h[3]	4h	-	0h[2]	1h[3]	4h	-	0h[2]	1h[3]	2h	4h	-	-	-	-	-	
AEs/SAEs	As Required																									
Comments	As Required																									
Epoch completion information																									X	

Key:

X = assessment to be recorded on clinical database

S = There is no CRF page created with the same name as these assessments, however results of these collections will be included in source documents and all pertinent information will also be included in the clinical database for all screened patients, either by means of CRF entries (i.e. AEs noted during physical examinations) or through data transfers (i.e. HIV/Hepatitis results) from the central lab.

* = assessment should be collected even if patient is prematurely discontinued from the study.

[1] Screening activities may occur over more than 1 visit; Results of screening assessments MUST be available prior to treating a patient.
[2] Assessments, including blood work, to be performed PRIOR TO DOSING.
[3] The “1 hour” time point refers to the estimated completion of the infusion of study drug (i.e. **at** the end of the infusion). The “1 hour” blood collection at visits 101 and 106 should be collected **within 5 minutes** post COMPLETION of the infusion. The “1 hour” vital signs assessment at all 4 dosing visits should be within 20 minutes of the COMPLETION of the infusion (see SOM for more details).
[4] Randomization scheduled on Day 1, prior to dosing, but may take place 24 hours in advance to accommodate preparation of study drug.

[5] FSH will be analyzed by the central lab for female study participants who have had oophorectomy in absence of a hysterectomy.

[6] All female study participants will have serum pregnancy testing as part of the central lab tests at all visits where pregnancy is assessed. IN ADDITION, a local urine sample will be collected on dosing days - prior to dosing -and analyzed at the site. Urine results collected on dosing days MUST BE available and confirmed as negative prior to dose administration.

[9] Measurements will only be conducted at a subset of trained investigational sites. These assessments may be performed during the screening period if the patient has already passed the inclusion and exclusion criteria, including ABI and 6MWT. See SOM for time windows and details for these assessments.

[10] The site will contact patients who do not return for their end of study visit, but have not withdrawn consent, approximately 140 days after their last dose of study medication, to capture any AEs or SAEs which occurred since their last visit. This contact should be documented in the source documents, and any AEs noted should be captured in the AE CRF.

[11] The end-of-study visit may be prolonged for any patient who has positive ADA values at the day 225 visit. See Section 8.8.1 for details.

8.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the patient's representative gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible, given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the patient agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the patient.

Ensure patients are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

Refer to the SOM for a complete list of ICFs included in this study.

8.3 Patient screening

It is permissible to re-screen a patient if s/he fails the initial screening or falls outside of the screening window; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

Information on what data should be collected for screening failures is outlined in the SOM.

8.4 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the SOM.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.5 Efficacy / Pharmacodynamics

Pharmacodynamic measurements will be assessed at the timepoints defined in the Assessment Schedule.

8.5.1 6-minute walk test

Maximum walking distance as assessed by the 6MWT will be used to evaluate functional capacity of PAD patients participating in this study.

In addition to the PD assessment of maximum walking distance, data generated from the 6MWT will also be used to evaluate pain-free walking distance.

Details of the 6MWT will be provided in the SOM, and sites will be provided additional training videos and manuals specific to the conduct and data collection of the 6MWT.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment Schedule (Section 8.1) detailing when each assessment is to be performed.

8.6.1 Physical examination

See the SOM for details.

8.6.2 Vital signs

- Body temperature
- Blood pressure
- Pulse rate
- Respiratory rate

See the SOM for details.

8.6.3 Height and weight

- Height
- Body weight
- BMI will be calculated as (Body weight (kg) / [Height (m)]^2)

See the SOM for details.

8.6.4 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an AE and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should be contacted.

Patients should be instructed to fast for at least 8 hours prior to scheduled serum lipid panel collections. Fasting is not required prior to other scheduled lab collections.

Details regarding collection methods and processing are outlined in the Central Laboratory Manual.

Hematology

Hemoglobin, hematocrit, PTT, PT/INR, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured.

Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed. Microscopy, WBC, RBC and sediments will also be assessed in case of an abnormal dipstick test.

Coagulation panel

D-dimer, fibrinogen, PTT, PT/INR will be measured as part of the safety labs conducted at the central lab.

8.6.5 Electrocardiogram

Full details of all procedures relating to the ECG collection and reporting are contained in the SOM.

PR interval, QRS duration, and QT intervals will be assessed.

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Clinically significant abnormalities must be reported in the AE CRF.

8.7 Pharmacokinetics

8.7.1 Pharmacokinetics

PK samples will be collected at the timepoints defined in the Assessment Schedule (Section 8.1). Follow instructions outlined in the SOM and Central Laboratory Manual regarding sample collection, numbering, processing and shipment. See Section 8.9 regarding the potential use of residual samples.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. The changes will be communicated to participating sites in a protocol or SOM amendment.

PK samples will be obtained and evaluated in all patients at all dose levels except the placebo group.

Concentrations will be expressed in mass per volume units.

Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol.

The following PK parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): Cmax, Tmax, AUClast, AUCtau, T1/2, Vz/F and CL/F from the serum concentration-time data. Some of these PK parameters are exploratory in this study.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal serum elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUCinf and CL/F.

Corporate Confidential Information

9 Safety monitoring

9.1 Adverse events

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign, including abnormal laboratory findings, symptom or disease) in a patient after *providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from screening or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. The severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. its relationship to the study treatment
   - Yes or
   - No
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.

   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of Investigator Notifications. Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

*Refer to the SOM for data capture methodology regarding AE collection for patients that fail screening.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any AE [appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)] which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect in offspring
- requires inpatient hospitalization or prolongation of existing hospitalization, UNLESS the hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (e.g. critical limb ischemia)
  - elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study and has not worsened since the start of study drug;
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission;
  - social reasons and respite care in the absence of any deterioration in the patient's general condition.
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

NOTE that all malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to ICH-E2D Guideline 2004).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to ICH-E2D Guideline 2004).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 9.2.2.

9.2.2 SAE reporting

Screen Failures

Details collected about Screen Failures is outlined in the SOM.

SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

Randomized / Treated Patients

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 140 days after the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence as described below.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the IB and is thought to be related to the study treatment, a CMO&PS Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the SOM regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 1should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 15-1-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the patient. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

- If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug [refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
- Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and GGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic. Retesting should be continued up to resolution.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 15-3.
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.4 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record CRF. Study treatment errors are only to be reported to CMO&PS department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the AE CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis CMO&PS. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Guidance for capturing study treatment errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

Reproductive toxicity and teratogenicity data are not available for the investigational drug at this time, therefore no guidelines on therapeutic recommendations in case of pregnancy are available. This study enrolls women who are considered to be of non-child-bearing potential, thus pregnancy is not an expected outcome for any female study participant. However, in the case that a pregnancy in a female study participant should occur, please follow the below reporting guidelines.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis CMO& PS Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

9.7 Prospective suicidality assessment

The intended target of LLG783 is not the central nervous system (CNS), nor is the drug intended to be used for a neurologic or psychiatric indication. Given that LLLG783 is a monoclonal antibody CCI its concentration in CNS is expected to be extremely low due to low blood brain barrier permeability. In non-clinical studies, there were no findings suggesting a relevant CNS effect. Therefore, in consideration of the target, potential for CNS penetration and findings in nonclinical studies, it is concluded that no suicidality assessment is needed in this study.

9.8 Early phase safety monitoring

The Investigator will monitor AEs in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e.g., e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. electronic CRFs) with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis or a CRO working on behalf of Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the electronic CRFs using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the electronic CRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the SOM and Assessment schedule (Section 8.1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

10.3 Database management and quality control

Novartis staff or CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or CRO working on behalf of Novartis, who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis or a designated CRO.

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

Not required.

11 Data analysis

The analysis will be conducted on all patient data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) received.

The safety analysis set will include all patients that received any study drug.

The PK analysis set will include all patients with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all patients with available PD data and no protocol deviations with relevant impact on PD data.

11.2 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and patient. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and patient.

11.3 Treatments

Data for study drug administration and concomitant therapies will be listed by treatment group and patient.

11.4 Analysis of the primary variable(s)

11.4.1 Primary Variable(s)

The primary efficacy endpoint is maximum walking distance (MWD) from the 6-minute walk test.

11.4.2 Statistical model, hypothesis, and method of analysis

The change from baseline in MWD will be analyzed in a repeated measures mixed effects model with treatment, day (as a categorical variable), and the treatment-by-day interaction as fixed effects and baseline MWD as a covariate. The day-by-baseline MWD interaction may be included in the model as an additional covariate. An unstructured covariance structure will be used. Baseline will be taken from the screening 6-minute walk test.

The least-square mean change from baseline in MWD for each day will be estimated from the model for each treatment along with the treatment difference and the associated p-value and two-sided 80% confidence interval (CI).

From the Week 16 quantities, the following criteria will be assessed:

1. The lower confidence limit of the 80% CI for the treatment difference (LLG783 – placebo) is greater than 0.
2. The estimated treatment difference is greater than or equal to 50 meters.

The first criterion will address whether, with high certainty, LLG783 is superior to placebo in improvement in MWD. The second criterion will address whether the observed mean improvement in MWD over placebo is at least 50 meters, a threshold that is considered to represent highly competitive efficacy in this patient population.

11.4.3 Handling of missing values/censoring/discontinuations

The primary analysis will be based on all patients with a baseline MWD and at least one post-baseline MWD. Patients who undergo any lower extremity vascular interventions (angioplasty, stenting, or bypass surgery) before the Week 16 efficacy assessment or patients who drop out for other reasons before this assessment may be replaced to ensure 40 patients complete this primary endpoint assessment. Data from such patients will be included in the model for the primary analysis until the time of dropout or intervention; no imputation of the missing data will be performed for the primary analysis.

11.4.4 Summary statistics of safety

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment group, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on AEs will be displayed by treatment group and patient.

The number and percentage of patients with AEs will be tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple AEs within a body system is only counted once towards the total of this body system.

11.4.5 Sensitivity analyses

As sensitivity analyses, the same analysis described for the primary analysis will be performed using the last observation carried forward (LOCF) and worst observation carried forward (WOCF) approaches of imputation for missing MWD data.

Baseline maximum walk distance will be summarized separately for patients who complete the 6MWT at week 16 and those who drop out of the study prior to this assessment. Summary statistics will include N, mean, SD, minimum, median, and maximum. The p-value from a two-sample t-test comparing the baseline maximum walk distance between the two groups will be reported together with the summary.

The relationship between the maximum change in maximum walk distance and baseline maximum walk distance will be explored using a graphical and modeling approach. A simple linear regression line and the Pearson correlation, both for each treatment, will be overlaid onto a scatterplot. Additionally, a linear regression model for the maximum change in maximum walk distance with effects of treatment, baseline, and the treatment-by-baseline interaction will be fit, and the p-value for the test of the interaction effect will be reported. The relationship between change in maximum walk distance and change in ABI at week 16 will be explored in a similar fashion.

11.5 Analysis of secondary variable(s)

11.5.1 Pharmacokinetics

LLG783 serum concentrations will be listed by treatment, patient, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Pharmacokinetic parameters will be calculated as described in Section 8.7.1 and will be listed by treatment and patient and summarized by treatment and visit. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

11.5.3 Pain-free walk distance

The change from baseline in pain-free walking distance will be analyzed in a similar way to MWD as described in Section 11.4.2 and Section 11.4.3.

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

References are available upon request.

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15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case	
ALT or AST elevation with coagulopathy	• Discontinue the study treatment immediately Hospitalize, if clinically appropriate
ALT or AST elevation accompanied by symptoms	• Establish causality
Isolated ALT or AST elevation > 8 × ULN	• Complete CRFs per liver event guidance*
Jaundice	
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance*
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance*

*Liver event guidance for CRF completion is available in the Site Operations Manual

Note: In exceptional cases when a hepatologist considers a liver biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of hepatotoxicity.

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Specific Renal Alert Criteria and Actions

Additional specialized assessments are available to assess renal function or renal pathology. Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-1 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output • Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline)
Monitor patient regularly (frequency at investigator's discretion) until:	or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.