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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LLG783

CLLG783X2201

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

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"CLLG783X2201".**

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

Tables, Figures, Listings (TFL) details the presentation of the data, including shells of summary tables, figures and listings, and Programming Datasets Specification **(**PDS) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR and IA outputs.

1.2 Study reference documentation

Final study protocol (version v00) is available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives

1.3.1 Primary objective(s)

Primary objective(s)	Endpoints related to primary objectives

• To evaluate the safety and tolerability of LLG783 in subjects 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 subjects with PAD and intermittent claudication.	• Maximum walking distance assessed by 6-minute walk test (6MWT)

1.3.2 Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objectives

• To investigate the PK of LLG783 in subjects 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 subjects with PAD and intermittent claudication.	• Pain-free walking distance assessed by 6MWT

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1.4 Study design and treatment

This is a non-confirmatory, randomized, subject and investigator-blinded, placebo-controlled, parallel-group study in subjects with PAD and intermittent claudication.

Approximately 40 randomized subjects 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.

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

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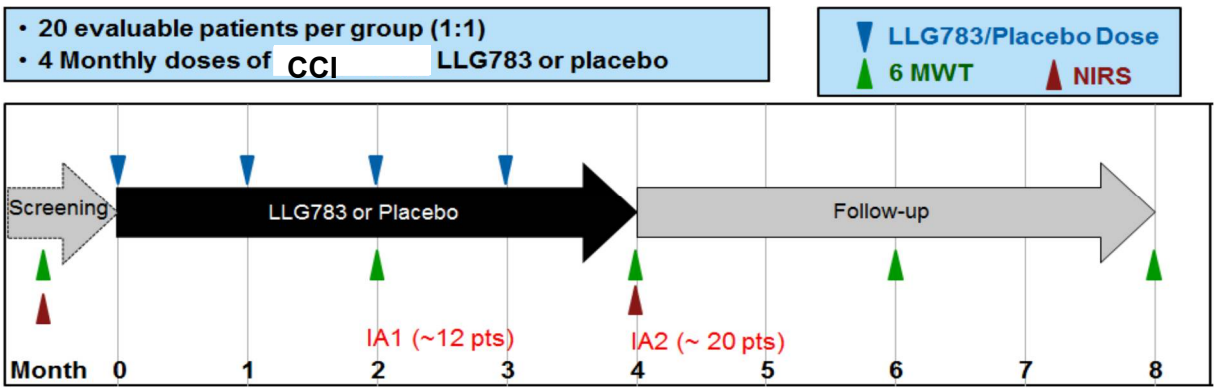
Figure 1-1 Study design



It is intended that the s.c. study participants would maintain the same assessment visit schedule as the i.v. dosed study participants.
Subjects who discontinue the study for reasons other than safety prior to the week 16 visit may be replaced to ensure ability to assess 40 subjects with a functional assessment after 16 weeks of exposure.

2 First interpretable results (FIR)

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FIR **Corporate Confidential Information** will focus on the following analyses:

1. Subject disposition **Corporate Confidential Information**
2. Demographics and baseline characteristics **Corporate Confidential Information**
3. Safety results **Corporate Confidential Information**
    - Number and percentage of subjects with adverse events by preferred term.
    - Overall incidence of AEs.
4. Efficacy results **Corporate Confidential Information**
    - Arithmetic mean (80% CI) of 6MWT parameters vs time profile by treatment.
    - MMRM model analysis of 6MWT parameters.
    - Model estimated means of 6MWT parameters over time.
5. Pharmacokinetic results for Plasma **Corporate Confidential Information**
    - Arithmetic mean (SD) concentration-time plot.
    - Summary statistics for PK parameters.
6. Immunogenicity Data **Corporate Confidential Information**

3 Interim analyses

There are 2 planned IAs in this study. It is planned to conduct the first IA (IA1) once approximately 12 subjects reach 8 weeks following the first dose. The purpose of IA1 will be to assess the PK of LLG783 to make a dose adjustment should the exposure be significantly lower or higher than expected.

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Unblinded IA results will be reviewed by the clinical team. The clinical team may communicate interim results (e.g. evaluation of efficacy criteria or information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

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Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns. In this case, the analyses as described in the sections below are conducted for the relevant endpoints.

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4 Statistical methods: Analysis sets

For subjects whose actual treatment received does not match the randomized treatment, the treatment actually received will be used for the analysis.

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

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

The PD analysis set will include all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from **PD** analysis set
COMD03	*Change in type or dosage of narcotic pain relievers; OR Change in type or dosage of PAD specific symptom-relief drugs prior to week 16 of study.*	
Inc05	*Deviation from inclusion criterion 5 – Moderately impaired ambulatory function due primarily to PAD and maximum walk distance between 50 and 400 meters.*	
Exc02	*Deviation from exclusion criterion 2 – Pregnant or nursing (lactating) women.*	
Exc05b	*Deviation from exclusion criterion 05b – Chronic heart failure New York Heart Association Class III or IV.*	
Exc14	*Deviation from exclusion criterion 14 – Patients unable to hold all narcotic pain relievers for 24 hours prior to performance of the 6MWT.*	
Inc03	*Deviation from inclusion criterion 3 - On stable medical therapy for at least 4 weeks prior to the screening visit.*	
Exc03	*Deviation from exclusion criterion 3 – Patients who meet the specific PAD related exclusion criteria.*	

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

Dose adjustment might occur as part of the IA1 safety and tolerability conclusions. In case of dose adjustment occurring during the study, subjects will be analyzed under first dose received, censoring any observations post dose adjustment (if any) in statistical models and descriptive summaries. Further updates on the SAP analysis strategy described below may be needed, depending on the findings of the IA1 and the proposed changes to the dosing strategy.

5 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK analysis set will be included in the PK data analysis.

In case of dose adjustment occurring during the study, subjects will be analyzed under first doses received, censoring any observations post dose adjustment (if any) in descriptive summaries.

5.1 Variables

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If data permit and as applicable, the following pharmacokinetic parameters for the parent LLG783 will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher) from the serum concentration data.

- PK parameters related to secondary objectives:
  - AUCinf, AUClast, AUC0-t, AUC0tau, Cmax, Tmax.

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5.2 Descriptive analyses

LLG783 serum concentrations will be listed by treatment, subject, 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 above the ULOQ) and reported as zero. Pharmacokinetic parameters will be listed by treatment and subject 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.

Arithmetic mean (SD) serum concentration by time will be plotted on linear-linear and log-linear scale (all treatment groups in the same graph).

Overlaying individual serum concentration by time profile, by treatment will be plotted (one graph per treatment group, all subjects in the same graph) on linear-linear and log-linear scale.

Individual serum concentration by time profile, by subject will be plotted on linear-linear and log-linear scale (one graph per treatment group and subject).

6 Statistical methods for Efficacy/Pharmacodynamic (PD) parameters

All subjects within the PD analysis set will be included in the PD data analysis.

In case of dose adjustment occurring during the study, subjects will be analyzed under first doses received, censoring any observations post dose adjustment (if any) in statistical models and descriptive summaries.

6.1 Primary objective

To evaluate the effect of LLG783 on functional capacity after 3 months of treatment in subjects with PAD and intermittent claudication.

6.1.1 Variables

The primary efficacy endpoint is the Maximum walking distance (MWD) defined as the total distance walked in 6 minutes as assessed by the 6MWT and will be used to evaluate functional capacity of PAD subjects participating in this study.

Change from baseline in MWD will also be derived. Baseline will be taken from the screening 6-minute walk test.

6MWT data will be excluded from primary and secondary analyses under below conditions:

- within 24 hours after narcotic pain medication
- the very first 6MWT after the adverse event of COPD exacerbation
- all tests after post baseline stent or angioplasty procedures
- Lap distance for the 6MWT significantly shorter than the recommended length of 50-70m

6.1.2 Descriptive analyses

Maximum walking distance (MWD) and change from baseline in MWD will be listed by treatment, subject and visit. Summary statistics will be provided for raw and change from baseline by treatment and visit/time and will include sample size, mean (arithmetic), SD, median, minimum, maximum.

6.1.2.1 Graphical presentation of results

Arithmetic mean (80% CI) of raw MWD and change from baseline in MWD will be plotted by visit and treatment. Spaghetti plots of raw MWD and change from baseline in MWD of all individuals will be given by treatment.

6.1.3 Statistical model, assumptions and hypotheses

The change from baseline in MWD will be analyzed in a repeated measure mixed effects model with treatment, visit and the treatment-by-visit interaction as fixed effects and baseline MWD as a covariate. The visit-by-baseline MWD interaction may be included in the model as an additional covariate. An unstructured residual covariance structure will be used, if possible, otherwise if an unstructured covariance cannot be fitted, simpler structures will be explored.

The Least-Squares Mean (LSM) change from baseline in MWD for each visit 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 subject population.

6.1.3.1 Model checking procedures

Handling of missing values/censoring/discontinuations

The primary analysis will be based on all subjects with a baseline MWD and at least one post baseline MWD. Subjects who undergo any lower extremity vascular interventions (angioplasty, stenting, or bypass surgery) before the Week 16 efficacy assessment or subjects who drop out for other reasons before this assessment may be replaced to ensure 40 subjects complete this primary endpoint assessment. Data from such subjects 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.

6.1.3.2 Graphical presentation of results

Model estimated treatment means and difference in change from baseline in MWD will be plotted over time, by visit (all treatment groups in the same graph).

6.1.3.3 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 subjects 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 fitted, 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.

Depending on the assessment of the PK profiles and dose response of subjects on different dose levels (if any after IA1), it might be reasonable to assume same mean response for both doses (providing similar AUC in the PAD population as observed in healthy volunteers). In that case different dose levels can be combined in one treatment arm regardless of different dose level.

6.2 Secondary objectives

To evaluate the effect of LLG783 on symptomatic functional capacity after 3 months of treatment in subjects with PAD and intermittent claudication.

6.2.1 Variables

The secondary efficacy endpoint is the pain-free walking distance defined as the distance walked up to the point of onset of claudication symptoms as assessed by the 6MWT and will be used to evaluate symptomatic functional capacity of PAD subjects participating in this study.

Change from baseline in pain-free walking distance will also be derived. Baseline will be taken from the screening 6-minute walk test.

The exclusion rule of 6MWT defined in Section 6.1.1 will also apply to pain-free walking distance.

6.2.2 Descriptive analyses

Secondary endpoint will be listed and summarized in an equivalent way as described in Section 6.1.2.

6.2.3 Statistical model, assumptions and hypotheses

Secondary endpoint will be analyzed in an equivalent way as described in Section 6.1.3.

6.2.3.1 Model checking procedures

Model checking procedures for pain-free walking distance will be the same as for primary analysis, refer to Section 6.1.3.1.

6.2.3.2 Graphical presentation of results

Graphical presentation of results for pain-free walking distance will be the same as for primary analysis, refer to Section 6.1.3.2.

6.2.3.3 Sensitivity analyses

As sensitivity analyses, the same analysis described for the secondary analysis in Section 6.2.3, will be performed using the last observation carried forward (LOCF) and worst observation carried forward (WOCF) approaches of imputation for missing pain-free walking distance.

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7 Statistical methods for safety and tolerability data

All subjects within the Safety analysis set will be included in the safety data analysis.

In case of dose adjustment occurring during the study, safety analyses will be performed by two analysis periods: pre-dose adjustment period and post-dose adjustment period. All subjects will be summarized by dose received during each period.

7.1 Variables

Safety variables include adverse events, vital signs (body temperature, blood pressure, pulse rate, respiratory rate), height and weight, ECG intervals, laboratory measurements (hematology, clinical chemistry, urinalysis, coagulation panel), as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. 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 subject.

Treatment

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

Vital signs

All vital signs data will be listed by treatment, subject, 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.

Height and weight

All height and weight and BMI data will be listed by treatment, subject, and visit, as part of the vital signs panel.

ECG evaluations

All ECG data will be listed by treatment, subject 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, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

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

The number and percentage of subjects with adverse events by maximum severity of adverse events will be tabulated by body system and preferred term with a breakdown by treatment.

The number and percentage of subjects with adverse events classified as related to study drug will be tabulated by body system and preferred term with a breakdown by treatment.

ClinicalTrials.gov and EudraCT

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population and prepared internally by Novartis.

If for a same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Other safety evaluations

Immunogenicity

All immunogenicity results will be listed by subject and visit/time. Summary statistics will be provided by treatment and visit/time.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

8 Pharmacokinetic / pharmacodynamic relationships

All subjects within the PK/PD analysis set will be included in the PK/PD data analysis.

In case of dose adjustment occurring during the study, PK/PD analyses may be performed by two analysis periods: pre-dose adjustment period and post-dose adjustment period. All subjects will be summarized by dose received during each period.

In addition, relationship between LLG783 concentration or an appropriate PK parameter and MWD may be explored in a graphical and/or modeling approach.

9 Statistical methods for biomarker data

Handling of LLOQ and ULOQ

Biomarker data are reported as concentration results, measured using a specific assay with a working range defined by the two limits: Lower limit of quantification (LLOQ) and Upper limit of quantification (ULOQ). Values which fall below the LLOQ or above the ULOQ are reported as < LLOQ * dilution factor (dilution factor: if sample diluted and concentration measured still below LLOQ) and > ULOQ * dilution factor, respectively.

To ensure that biomarkers only have numerical values, censored values will be imputed as follows

- Values below the LLOQ are replaced by LLOQ/2.
- Values above the ULOQ are replaced by ULOQ.

Imputed values are used for summary statistics, inferential analyses and plots (with a special symbol). Values below LLOQ and values above ULOQ are shown as such in the listings. In the summary table, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.

If the proportion of imputed data is more than 20% for any treatment group at any time point, a footnote is added to the summary statistics table stating that the proportion of values outside the limits of quantification is more than 20% for some treatment groups at some time points and that in such cases summary statistics may be heavily biased.

If the proportion of imputed data for a given biomarker, across all treatment groups and time points, is more than 50%, no summary statistics are provided and the data are only listed.

If the proportion of imputed data for a given biomarker, across all treatment groups and time points, is more than 30%, no inferential analysis will be performed.

10 Reference list

1. Clinical Trial Protocol, CLLG783X2201 **Corporate Confidential Information**
2. Site Operations Manual for Protocol No. CLLG783X2201 **Corporate Confidential Information**
3. Investigator's Brochure for Protocol No. CLLG783X2201 **Corporate Confidential Information**