Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

LLG783

Trial Indication(s)

Peripheral artery disease (PAD) and intermittent claudication

Protocol Number

CLLG783X2201

Protocol Title

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

Clinical Trial Phase

Phase IIa

Phase of Drug Development

Phase IIa

Study Start/End Dates

20-Sep-2017 to 27-Dec-2018

Reason for Termination (If applicable)

NA

Study Design/Methodology

This was a non-confirmatory, randomized, participant and Investigator-blinded, placebo-controlled, parallel-arm study in participants with PAD and intermittent claudication. The study was planned to treat participants in a 1:1 ratio to receive 6 mg/kg of LLG783 or placebo as an intravenous infusion once every 4 weeks for a total of 4 doses over a period of 12 weeks or 3 months.

Centers

The study was conducted in Germany (4 sites), Taiwan (2 sites) and USA (2 sites).

Objectives:

Primary objective(s)

The primary objectives of this study were:

- To assess the safety and tolerability of LLG783 in participants 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 participants with PAD and intermittent claudication: Maximum walking distance (MWD) assessed by 6-minute walk test (6MWT)

Secondary objective(s)

The Secondary objectives of the study were:

- To investigate the pharmacokinetics (PK) of LLG783 in participants with PAD and intermittent claudication;
- To evaluate the effect of LLG783 on symptomatic functional capacity after 3 months of treatment in participants with PAD and intermittent claudication: Pain-free walking distance (PFWD) assessed by 6MWT

Test Product (s), Dose(s), and Mode(s) of Administration

LLG783 150 mg/mL concentrate solution for infusion/injection and placebo 0 mg/mL for iv administration.

Statistical Methods

- All safety variables were summarized with descriptive statistics for the safety analysis set. The safety analysis set included all participants that received any study treatment
- The primary efficacy endpoint was MWD, defined as the total distance walked in 6 minutes as assessed by the 6MWT and was used to evaluate functional capacity of PAD participants The change from baseline in MWD was analyzed in a mixed effect model repeat measurement (MMRM) with treatment, visit and the treatment-by-visit interaction as fixed effects and baseline MWD as a covariate. All participants with any available pharmacodynamics (PD) data, who received any study drug and experienced no protocol deviations with relevant impact on PD data were included in PD analysis set.

- The secondary efficacy endpoint, PFWD was defined as the distance walked up to the point of onset of claudication symptoms (pain) recorded during the 6MWT and was used to evaluate symptomatic functional capacity of PAD participants participating in this study. Secondary endpoint was analyzed in an equivalent way as described for primary efficacy endpoint.
- PK parameters for LLG783 were determined using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin v 6.8 from the serum concentration data. All participants with at least one available valid PK concentration measurement, who received any study treatment and experienced no protocol deviations with relevant impact on PK data.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

- Male and female participants 40 to 85 years of age (inclusive) at screening with clinical evidence of PAD and intermittent claudication (Fontaine stage II).
- On stable medical therapy for PAD and PAD symptoms, which could 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 were to be within the following ranges: body temperature between 35.0-37.5°C; systolic blood pressure, 90-159 mm Hg; 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 MWD between 50 and 400 meters (inclusive of these values) at the screening 6MWT

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 human chorionic gonadotropin (hCG) laboratory test.
- Participants who met any of the following PAD related criteria:
    - Participants who were actively attending and participating in a supervised exercise rehabilitation program (participants who had already completed such a program and remain symptomatic may be included).
    - Participants 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)
- 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 HbA1c greater than 9% as measured at screening.

- 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 or actively planned/scheduled lower extremity peripheral vascular interventions within the first 4 months after enrollment.
- Inability to hold all narcotic pain relievers for 24 hours prior to performance of the 6MWT

Participant Flow Table

	LLG783 iv 6 mg/kg n (%)	Placebo iv n (%)	All patients n (%)
Epoch: Screening	**N=23**	**N=23**	**N=46**
Patients			
Randomized	23 (100.0)	23 (100.0)	46 (100.0)
Completed	23 (100.0)	23 (100.0)	46 (100.0)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)
Epoch: Treatment	**N=23**	**N=23**	**N=46**
Patients			
Completed	22 (95.7)	22 (95.7)	44 (95.7)
Discontinued	1 (4.3)	1 (4.3)	2 (4.3)
Primary reason for discontinuation			
Adverse event		1 (4.3)	1 (2.2)
Patient decision	1 (4.3)		1 (2.2)

N = Number of patients entered the epoch

Baseline Characteristics

Demographic variable	LLG783 iv 6 mg/kg N=23 n (%)	Placebo iv N=23 n (%)	All patients N=46 n (%)
Age (years)			
Mean (SD)	67.0 (7.1)	66.3 (6.9)	66.7 (6.9)
Median	67.0	67.0	67.0
Range	52 - 80	54 - 81	52 - 81
Sex - n (%)			
Female	8 (35.0%)	5 (22.0%)	13 (28.0%)
Male	15 (65.0%)	18 (78.0%)	33 (72.0%)
Race - n (%)			
White	23 (100.0%)	21 (91.0%)	44 (96.0%)
Asian		2 (9.0%)	2 (4.0%)
Ethnicity - n (%)			
Not Hispanic or Latino	23 (100.0%)	23 (100.0%)	46 (100.0%)
MWD (m)			
Mean (SD)	317.3 (62.0)	311.3 (84.0)	314.3 (73.0)
Median	325.7	335.0	331.3
Range	165.5 - 390.0	114.0 - 397.0	114.0 - 397.0
PFWD (m)			
Mean (SD)	160.7 (79.4)	156.0 (86.7)	158.3 (82.2)
Median	149.4	148.0	148.7
Range	46.7 - 359.7	39.8 - 394.0	39.8 - 394.0

Primary Outcome Result(s)

Number of Participants reported with any adverse events (AEs), study drug-related AEs, serious AEs, AEs leading to discontinuation, deaths: Safety Analysis Set

Category	LLG783 iv 6 mg/kg N = 23 nE, nS (%)	Placebo iv N = 23 nE, nS (%)	All patients N = 46 n (%)
AEs, Patients with AEs	58, 18 (78.3)	37, 17 (73.9)	95, 35 (76.1)
AEs of mild intensity	25, 15 (65.2)	25, 14 (60.9)	50, 29 (63.0)
AEs of moderate intensity	32, 14 (60.9)	10, 5 (21.7)	42, 19 (41.3)
AEs of severe intensity	1, 1 (4.3)	2, 2 (8.7)	3, 3 (6.5)
Study drug-related AEs	4, 4 (17.4)	6, 4 (17.4)	10, 8 (17.4)
SAEs	1, 1 (4.3)	2, 2 (8.7)	3, 3 (6.5)
AEs leading to discontinuation of study treatment	0	1, 1 (4.3)	1, 1 (2.2)
Study drug-related AEs leading to discontinuation of study treatment	0	0	0

N= number of patients studied.
nE = number of events in the category.
nS = number of patients with at least one AE in the category.
% is based on the number of patients.
Only AEs occurring at or after first drug intake were included.
MedDRA v 21.1.

There were no deaths reported in the study

Change from baseline in MWD: PD analysis set

Parameter (unit): MWD (m) Visit	Treat-ment	n	Unadjusted arithmetic mean (80% CI)	Adjusted arithmetic mean (80% CI)	Difference (LLG783-Placebo)	80% CI	P-value
Day 57 (Month 2)	LLG783 iv 6 mg/kg	22	21.22 (46.83)	20.88 (9.68, 32.08)	-3.18	(-19.82, 13.46)	0.804
	Placebo	18	22.31 (31.23)	24.06 (11.78, 36.35)			
Day 113 (Month 4)	LLG783 iv 6 mg/kg	22	19.44 (54.84)	19.10 (5.30, 32.90)	-17.74	(-38.03, 2.55)	0.261
	Placebo	19	36.27 (45.11)	36.84 (21.99, 51.70)			
Day 169 (Month 6)	LLG783 iv 6 mg/kg	22	17.18 (53.52)	16.84 (3.15, 30.53)	-17.05	(-37.32, 3.22)	0.280
	Placebo	18	33.61 (42.75)	33.89 (18.96, 48.82)			
EOS (Month 8)	LLG783 iv 6 mg/kg	21	4.59 (47.79)	4.79 (-7.47, 17.04)	-22.64	(-40.77, -4.52)	0.112
	Placebo	18	27.17 (36.59)	27.43 (14.09, 40.77)			

P-value was calculated from a two-sided test. P-value of ≤ 0.2 was considered significant.
Baseline was taken from the screening 6MWT.

Secondary Outcome Result(s)

Change from baseline in PFWD: PD analysis set

Parameter (unit): PFWD (m) Visit	Treat-ment	n	Unadjusted arithmetic mean (80% CI)	Adjusted arithmetic mean (80% CI)	Difference (LLG783-Placebo)	80% CI	P-value
Day 57 (Month 2)	LLG783 iv 6 mg/kg	22	49.60 (90.10)	51.23 (27.00, 75.45)	-7.06	(-42.99, 28.87)	0.799
	Placebo	18	59.74 (100.58)	58.29 (31.78, 84.79)			
Day 113 (Month 4)	LLG783 iv 6 mg/kg	22	43.14 (101.35)	44.77 (20.52, 69.02)	-12.33	(-48.00, 23.35)	0.655
	Placebo	19	60.46 (86.77)	57.09 (30.97, 83.22)			
Day 169 (Month 6)	LLG783 iv 6 mg/kg	22	46.65 (133.42)	48.27 (17.22, 79.32)	-36.46	(-82.63, 9.71)	0.310
	Placebo	18	87.62 (108.34)	84.73 (50.58, 118.88)			
EOS (Month 8)	LLG783 iv 6 mg/kg	21	40.20 (107.79)	41.44 (14.73, 68.16)	-64.05	(-103.56, -24.54)	0.041
	Placebo	18	108.36 (98.61)	105.49 (76.41, 134.57)			

P-value was calculated from a two-sided test. P-value of ≤ 0.2 was considered significant.
Baseline was taken from the screening 6MWT.

Pharmacokinetic parameters for LLG783: PK analysis set

PK parameter (unit)	Visit	LLG783 6 mg/kg N=23
Cmax (µg/mL)	Day 1	220 ± 109 (49.3%) [23]
	Day 85	291 ± 143 (49.0%) [23]
Tmax (day)	Day 1	0.0833 (0.0417 - 3.01) [23]
	Day 85	0.0833 (0.0431 - 9.94) [23]
Clast (uµg/mL)	Day 1	30.1 ± 13.1 (43.3%) [23]
	Day 85	7.07 ± 11.1 (157.3%) [23]
Tlast (day)	Day 1	28.3 ± 0.893 (3.1%) [23]
	Day 85	103 ± 28.2 (27.4%) [23]
AUCtau (day×µg/mL)	Day 1	1740 ± 639 (36.7%) [23]
	Day 85	3310 ± 1260 (38.0%) [23]
CLss (L/day)	Day 85	0.185 ± 0.0629 (33.9%) [20]
Vss_obs (L)	Day 85	4.99 ± 2.38 (47.6%) [20]
T1/2 (day)	Day 85	23.3 ± 11.9 (51.0%) [20]

Statistics are presented as Mean ± SD (CV%) [n]
CV% = Coefficient of variation (%) = sd/mean×100
For Tmax, Statistics are presented as Median (Min-Max) [n]

Safety Results

Adverse Events by System Organ Class regardless of study treatment relationship (Safety analysis set)

Primary system organ class	LLG783 iv 6 mg/kg N = 23 n (%)	Placebo iv N = 23 n (%)	All patients N = 46 n (%)
Number of patients with at least one AE	**18 (78.3)**	**17 (73.9)**	**35 (76.1)**
Infections and infestations	9 (39.1)	6 (26.1)	15 (32.6)
Nervous system disorders	6 (26.1)	3 (13.0)	9 (19.6)
Gastrointestinal disorders	5 (21.7)	3 (13.0)	8 (17.4)
General disorders and administration site conditions	7 (30.4)	1 (4.3)	8 (17.4)
Musculoskeletal and connective tissue disorders	3 (13.0)	3 (13.0)	6 (13.0)
Vascular disorders	3 (13.0)	3 (13.0)	6 (13.0)
Cardiac disorders	3 (13.0)	2 (8.7)	5 (10.9)
Injury, poisoning and procedural complications	1 (4.3)	4 (17.4)	5 (10.9)
Investigations	4 (17.4)	0	4 (8.7)
Respiratory, thoracic and mediastinal disorders	3 (13.0)	1 (4.3)	4 (8.7)
Blood and lymphatic system disorders	1 (4.3)	2 (8.7)	3 (6.5)
Skin and subcutaneous tissue disorders	0	2 (8.7)	2 (4.3)
Metabolism and nutrition disorders	0	1 (4.3)	1 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (4.3)	1 (2.2)
Psychiatric disorders	1 (4.3)	0	1 (2.2)

A patient with multiple AEs was counted only once in the "at least one AE" row.
A patient with multiple AEs within a primary SOC was counted only once for that SOC and treatment.
Arranged in descending order of frequency (in "all patient" column) and alphabetically by SOC.
Only AEs occurring at or after first study treatment intake were included.
MedDRA v 21.1.

Most Frequently Reported AEs Overall by Preferred Term n (%)
Frequent adverse events (>5% in any arm) regardless of treatment relationship by preferred term (Safety analysis set)

Preferred term	LLG783 iv 6 mg/kg N = 23 n (%)	Placebo iv N = 23 n (%)	All patients N = 46 n (%)
Number of patients with at least one AE	**18 (78.3)**	**17 (73.9)**	**35 (76.1)**
Nasopharyngitis	5 (21.7)	4 (17.4)	9 (19.6)
Diarrhoea	3 (13.0)	1 (4.3)	4 (8.7)
Headache	2 (8.7)	2 (8.7)	4 (8.7)
Peripheral arterial occlusive disease	3 (13.0)	1 (4.3)	4 (8.7)
Back pain	2 (8.7)	1 (4.3)	3 (6.5)
Fatigue	2 (8.7)	1 (4.3)	3 (6.5)
Medical device site irritation (ActiGraph device)	3 (13.0)	0	3 (6.5)
Bradycardia	0	2 (8.7)	2 (4.3)
Oedema peripheral	2 (8.7)	0	2 (4.3)
Paraesthesia	0	2 (8.7)	2 (4.3)

A patient with multiple AEs was counted only once in the "at least one AE" row.
A patient with multiple AEs with the same PT was counted only once for that PT and treatment.
PTs were sorted in descending frequency, as reported in the "all patient" column.
Only AEs occurring at or after first study treatment intake were included.
MedDRA v 21.1.

Other Relevant Findings

NA

Conclusion:

While i.v. treatment with 6 mg/kg of LLG783 once a month for 3 months in patients with PAD and intermittent claudication was found to be safe and well-tolerated, there was no difference in the primary (MWD) and the secondary (PFWD) efficacy endpoint between the LLG783 and placebo arms. Assessment of exploratory biomarker/s and PK suggested that a sustained target engagement was achieved until at least Day 113.

Date of Clinical Trial Report

30 Aug 2019