Sponsor

Novartis

Generic Drug Name

LLF580

Trial Indication(s)

Not applicable

Protocol Number

CLLF580X2102

Protocol Title

A 12 week Phase Ib Randomized Investigator and Subject-Blinded Placebo Controlled Repeat-dose Study of LLF580

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1

Study Start/End Dates

Study Start Date: 26-Feb-2018 (Actual)
Primary Completion Date: 13-Nov-2019 (Actual)
Study Completion Date: 13-Nov-2019 (Actual)

Study Design/Methodology

This was a non-confirmatory, multicenter, randomized, investigator- and subject blinded, placebo-controlled safety study in obese subjects with moderate hypertriglyceridemia, administering LLF580 or placebo subcutaneously with repeated dosing over 3 months.

Centers

United States (7)

Objectives:

Primary objective

To assess the safety and tolerability in obese subjects following repeated dosing of LLF580 by subcutaneous (SC) injection over 12 weeks

Secondary objectives

To assess the effects of LLF580 on lipid profiles.
To assess the potential effects of LLF580 on bone biomarkers
To assess the effects of LLF580 on weight

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

LLF580 100 mg and placebo (liquid in vial) were prepared by Novartis and supplied to the Investigative site as an open labeled bulk medication. LLF580 300 mg (3 mL of LLF580 at 100 mg/mL) was administered subcutaneously in the upper, outer arm every 4 weeks for 3 doses.

Statistical Methods

The primary variables were AEs, vital signs, and clinical laboratory evaluations measured by the central lab, including clinical chemistries (e.g. electrolytes, renal, and LFTs). All information obtained on AEs were displayed by treatment group and subject. All the other variables were listed by treatment group, subject, and visit/time.

The secondary pharmacodynamic endpoints included triglycerides (fasting), total cholesterol, LDL-C, HDL-C, weight, BMI, and waist circumference. The natural logarithm of the ratio to baseline of these variables (fasting triglyceride, total cholesterol, LDL-C, HDL-C) was used as a dependent variable for a MMRM. The model included fixed effects for treatment, time, and treatment by time interaction, log(baseline) value, and log(baseline) by time interaction. Percent change from baseline in weight, and change from baseline in waist circumference were used as the dependent variable in the same MMRM model with corresponding baseline values replacing the log (baseline).

The secondary pharmacodynamic endpoints also included biomarkers of bone resorption (urine NTX-1 and serum CTX-1) and biomarkers of bone formation (serum BSAP, P1NP, OC) after 12 weeks of treatment. The natural logarithm of the ratio to baseline were analyzed by a mixed effect model with repeated measurement (MMRM) model. Least square mean ratio to baseline was estimated for each treatment by time combination along with the corresponding 95% confidence interval (the mean ratio to baseline for all of the tables are actually 100*mean ratio to baseline).

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria

- Male and female subjects aged 18 to 65 years.
- Body mass index within the range of 30 to 45 kg/m2, inclusive, with ethnic adjustment (≥ 27.5 kg/m2 for Asian individuals).
- Fasting triglyceride 150 - 500 mg/dL (1.69 - 5.65 mmol/L), inclusive, at screening.

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

Key exclusion criteria

- History of hepatobiliary disease, cholelithiasis, or biliary sludge by history or at screening ultrasound, coagulopathies, hepatic encephalopathy, esophageal varices, or porticaval shunt.
- Liver disease or liver injury as indicated by abnormal liver function tests (ALT, AST, ALP, or serum bilirubin) above 2.5 times upper limit of normal (ULN) at screening or baseline.
- Chronic infection with Human Immunodeficiency Virus (HIV), Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a subject. Subjects with a positive HCV antibody test must have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA must be excluded.
- Fasting triglycerides greater than 500 mg/dL [5.65 mmol/L], or concomitant use of drug treatment for hypertriglyceridemia (fibrates, omega-3 fatty acids, nicotinic acid).
- History of pancreatic injury or pancreatitis, or other pancreatic disease. Amylase or lipase above ULN at screening or amylase above ULN at baseline.
- History of hypersensitivity to drugs of similar biological class, FGF21 protein analogue, or Fc fusion proteins.
- History of bone disorders including but not limited to osteoporosis, osteopenia, osteomalacia, or serum vitamin D level is below the lower limit of the normal range at screening.
- Contraindications to MRI.
- Change in body weight (more than 5% self-reported or 5 kg self- reported change during the previous 3 months from screening).
- Use of weight loss drugs: Orlistat (Xenical, Alli), lorcaserin (Belviq), phentermine-topiramate (Qsymia), naltrexone-bupropion (Contrave), or liraglutide (Victoza or Saxenda) or other glucagon-like peptide-1 (GLP1) receptor agonists (exenatide (Byetta/Bydureon), lixisenatide (Luxumia), albiglutide (Tanzeum) or dulaglutide (Trulicity) or others).
- Enrollment in a diet, weight loss or exercise programs with the specific intent of losing weight, within 3 months prior to baseline visit, or clinical diagnosis of any eating disorder was also an exclusion.

• 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 120 days after stopping medication.

Participant Flow Table

Subject disposition- n (percent) of subjects (treatment epoch)

	LLF580 300 mg N=30 n (%)	Placebo N=31 n (%)	Total N=61 n (%)
Subjects			
Completed	25 (83.3)	26 (83.9)	51 (83.6)
Discontinued	5 (16.7)	5 (16.1)	10 (16.4)
Primary reason for discontinuation			
Adverse event	2 (6.7)	1 (3.2)	3 (4.9)
Lost to Follow-up	0 (0.0)	1 (3.2)	1 (1.6)
Physician decision	1 (3.3)	1 (3.2)	2 (3.3)
Subject/Guardian Decision	2 (6.7)	2 (6.5)	4 (6.6)

N = Number of subjects entered the Epoch

Baseline Characteristics

Subject demographics (Safety analysis set)

		LLF580 300 mg N=30	Placebo N=31	Total N=61
Age (years)	Mean (SD)	46.7 (10.67)	44.3 (12.28)	45.5 (11.48)
	Median	49.0	44.0	47.0
	Range	[23,64]	[21,63]	[21,64]
Sex - n (%)	Male	14 (46.7)	16 (51.6)	30 (49.2)
	Female	16 (53.3)	15 (48.4)	31 (50.8)
Race - n (%)	American Indian or Alaska Native	1 (3.3)	0 (0.0)	1 (1.6)
	Black or African American	4 (13.3)	5 (16.1)	9 (14.8)
	White	23 (76.7)	26 (83.9)	49 (80.3)
	Other	2 (6.7)	0 (0.0)	2 (3.3)

Primary Outcome Result(s)

Overall incidence of AEs - number of events and number of subjects (Safety analysis set)

	LLF580 300 mg N=30 nE, nS (%)	Placebo N=31 nE, nS (%)	Total N=61 nE, nS (%)
AEs, Subjects with AEs	157, 28 (93.3)	76, 24 (77.4)	233, 52 (85.2)
AEs of Grade 1	122, 28 (93.3)	64, 23 (74.2)	186, 51 (83.6)
AEs of Grade 2	28, 14 (46.7)	8, 8 (25.8)	36, 22 (36.1)
AEs of Grade 3	6, 4 (13.3)	3, 2 (6.5)	9, 6 (9.8)
AEs of Grade 4	1, 1 (3.3)	1, 1 (3.2)	2, 2 (3.3)
Study-drug related AEs	83, 23 (76.7)	24, 10 (32.3)	107, 33 (54.1)
Serious AEs	2, 2 (6.7)	3, 1 (3.2)	5, 3 (4.9)
AEs leading to discontinuation of study treatment	4, 2 (6.7)	1, 1 (3.2)	5, 3 (4.9)
Study-drug related AEs leading to discontinuation of study treatment	4, 2 (6.7)	0, 0 (0.0)	4, 2 (3.3)

N = number of subjects studied
nE = number of AE events in the category
nS = number of subjects with at least one AE in the category
% is based on the number of subjects

Secondary Outcome Result(s)

Analysis of Ratio to Baseline in Triglycerides: comparison between treatment groups by time point (Primary PD analysis set)

		Least square means ratio to baseline (95% CI)		Comparison of LS means LLF580 vs Placebo		
LLF580 vs Placebo	**Visit**	**LLF580**	**Placebo**	**Ratio**	**95% CI**	**P-Value**
LLF580 300 mg (n=24) vs Placebo (n=25)	Analysis Day 85	54.8 (48.2, 62.4)	94.1 (83.0, 106.8)	58.3	(48.6, 69.8)	<.001

Analysis of Ratio to Baseline in Total Cholesterol: comparison between treatment groups by time point (Primary PD analysis set)

		Least square means ratio to baseline (95% CI)		Comparison of LS means LLF580 vs Placebo		
LLF580 vs Placebo	**Visit**	**LLF580**	**Placebo**	**Ratio**	**95% CI**	**P-Value**
LLF580 300 mg (n=24) vs Placebo (n=25)	Analysis Day 85	91.3 (86.6, 96.3)	98.4 (93.5, 103.7)	92.8	(86.2, 99.9)	0.047

Analysis of Ratio to Baseline in LDL: comparison between treatment groups by time point (Primary PD analysis set)

		Least square means ratio to baseline (95% CI)		Comparison of LS means LLF580 vs Placebo		
LLF580 vs Placebo	**Visit**	**LLF580**	**Placebo**	**Ratio**	**95% CI**	**P-Value**
LLF580 300 mg (n=24) vs Placebo (n=25)	Analysis Day 85	89.9 (83.8, 96.5)	99.5 (92.8, 106.7)	90.4	(81.8, 99.8)	0.046

Analysis of Ratio to Baseline in HDL: comparison between treatment groups by time point (Primary PD analysis set)

		Least square means ratio to baseline (95% CI)		Comparison of LS means LLF580 vs Placebo		
LLF580 vs Placebo	**Visit**	**LLF580**	**Placebo**	**Ratio**	**95% CI**	**P-Value**
LLF580 300 mg (n=24) vs Placebo (n=25)	Analysis Day 85	122.2 (116.0, 128.7)	100.6 (95.6, 105.9)	121.4	(112.8, 130.6)	<.001

Analysis of Ratio to Baseline in Bone Specific Alkaline Phosphatase: comparison of treatment groups by time point (Secondary Safety Analysis Set)

		Least square means ratio to baseline (95% CI)		Comparison of LS means LLF580 vs Placebo		
LLF580 vs Placebo	Visit	LLF580	Placebo	Ratio	95% CI	P-Value
LLF580 300 mg (n=24) vs Placebo (n=26)	Analysis Day 85	93.3 (89.0, 97.8)	98.4 (94.0, 103.1)	94.8	(88.7, 101.3)	0.110

Analysis of Ratio to Baseline in Osteocalcin: comparison of treatment groups by time point (Secondary Safety Analysis Set)

		Least square means ratio to baseline (95% CI)		Comparison of LS means LLF580 vs Placebo		
LLF580 vs Placebo	Visit	LLF580	Placebo	Ratio	95% CI	P-Value
LLF580 300 mg (n=24) vs Placebo (n=26)	Analysis Day 85	84.9 (80.3, 89.7)	105.8 (100.2, 111.6)	80.3	(74.3, 86.8)	<.001

Analysis of Ratio to Baseline in P1NP: comparison of treatment groups by time point (Secondary Safety Analysis Set)

		Least square means ratio to baseline (95% CI)		Comparison of LS means LLF580 vs Placebo		
LLF580 vs Placebo	**Visit**	**LLF580**	**Placebo**	**Ratio**	**95% CI**	**P-Value**
LLF580 300 mg (n=24) vs Placebo (n=26)	Analysis Day 85	91.6 (85.1, 98.6)	107.4 (99.9, 115.3)	85.3	(76.9, 94.6)	0.003

Analysis of Ratio to Baseline in CTX-1: comparison of treatment groups by time point (Secondary Safety Analysis Set)

		Least square means ratio to baseline (95% CI)		Comparison of LS means LLF580 vs Placebo		
LLF580 vs Placebo	**Visit**	**LLF580**	**Placebo**	**Ratio**	**95% CI**	**P-Value**
LLF580 300 mg (n=24) vs Placebo (n=26)	Analysis Day 85	112.9 (101.0, 126.2)	105.2 (94.4, 117.3)	107.3	(91.7, 125.5)	0.371

Analysis of Ratio to Baseline in NTX-1: comparison of treatment groups by time point (Secondary Safety Analysis Set)

		Least square means ratio to baseline (95% CI)		Comparison of LS means LLF580 vs Placebo		
LLF580 vs Placebo	**Visit**	**LLF580**	**Placebo**	**Ratio**	**95% CI**	**P-Value**
LLF580 300 mg (n=24) vs Placebo (n=25)	Analysis Day 84	126.9 (108.6, 148.3)	107.4 (92.2, 125.0)	118.2	(95.1, 147.0)	0.129

Analysis of Percentage of Weight Change from Baseline: comparison between treatment groups by time point (Primary PD Analysis Set)

		Least square means ratio to baseline (95% CI)		Comparison of LS means LLF580 vs Placebo		
LLF580 vs Placebo	**Visit**	**LLF580**	**Placebo**	**Ratio**	**95% CI**	**P-Value**
LLF580 300 mg (n=25) vs Placebo (n=26)	Analysis Day 84	0.46 (-0.97, 1.88)	1.23 (-0.18, 2.63)	-0.77	(-2.78, 1.24)	0.446

Safety Results

All-Cause Mortality

	LLF580 300 mg N = 30	Placebo N = 31	Total N = 61
Arm/Group Description	LLF580 every 28 days * 3	Placebo to LLF580 every 28 days * 3	Total
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of approx. 1.5 years.
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (22.1)

Assessment Type for Table Default Systematic Assessment

	LLF580 300 mg N = 30	**Placebo N = 31**	**Total N = 61**
Arm/Group Description	LLF580 every 28 days * 3	Placebo to LLF580 every 28 days * 3	Total
Total participants affected	2 (6.67%)	1 (3.23%)	3 (4.92%)
Hepatobiliary disorders			
Cholecystitis	1 (3.33%)	0 (0.00%)	1 (1.64%)
Infections and infestations			
Pneumonia	0 (0.00%)	1 (3.23%)	1 (1.64%)
Sepsis	0 (0.00%)	1 (3.23%)	1 (1.64%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Burkitt's lymphoma	1 (3.33%)	0 (0.00%)	1 (1.64%)

Respiratory, thoracic and mediastinal disorders			
Respiratory failure	0 (0.00%)	1 (3.23%)	1 (1.64%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of approx. 1.5 years.
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	LLF580 300 mg N = 30	**Placebo N = 31**	**Total N = 61**
Arm/Group Description	LLF580 every 28 days * 3	Placebo to LLF580 every 28 days * 3	Total
Total participants affected	28 (93.33%)	24 (77.42%)	52 (85.25%)

Blood and lymphatic system disorders			
Lymphadenopathy	1 (3.33%)	0 (0.00%)	1 (1.64%)
Congenital, familial and genetic disorders			
Accessory spleen	0 (0.00%)	1 (3.23%)	1 (1.64%)
Endocrine disorders			
Thyroid mass	0 (0.00%)	1 (3.23%)	1 (1.64%)
Gastrointestinal disorders			
Abdominal discomfort	2 (6.67%)	0 (0.00%)	2 (3.28%)
Abdominal distension	1 (3.33%)	1 (3.23%)	2 (3.28%)
Abdominal pain	2 (6.67%)	1 (3.23%)	3 (4.92%)
Abdominal pain upper	1 (3.33%)	1 (3.23%)	2 (3.28%)
Anorectal discomfort	1 (3.33%)	0 (0.00%)	1 (1.64%)
Constipation	2 (6.67%)	0 (0.00%)	2 (3.28%)
Diarrhoea	8 (26.67%)	4 (12.90%)	12 (19.67%)
Dumping syndrome	1 (3.33%)	0 (0.00%)	1 (1.64%)

Dyspepsia	4 (13.33%)	1 (3.23%)	5 (8.20%)
Eructation	1 (3.33%)	0 (0.00%)	1 (1.64%)
Faeces discoloured	1 (3.33%)	0 (0.00%)	1 (1.64%)
Frequent bowel movements	1 (3.33%)	0 (0.00%)	1 (1.64%)
Gastritis	1 (3.33%)	0 (0.00%)	1 (1.64%)
Gastrooesophageal reflux disease	3 (10.00%)	0 (0.00%)	3 (4.92%)
Haemorrhoids	2 (6.67%)	0 (0.00%)	2 (3.28%)
Nausea	18 (60.00%)	2 (6.45%)	20 (32.79%)
Vomiting	9 (30.00%)	1 (3.23%)	10 (16.39%)
General disorders and administration site conditions			
Chills	1 (3.33%)	0 (0.00%)	1 (1.64%)
Energy increased	0 (0.00%)	1 (3.23%)	1 (1.64%)
Fatigue	2 (6.67%)	0 (0.00%)	2 (3.28%)
Feeling jittery	1 (3.33%)	0 (0.00%)	1 (1.64%)
Influenza like illness	1 (3.33%)	0 (0.00%)	1 (1.64%)
Injection site bruising	1 (3.33%)	0 (0.00%)	1 (1.64%)

Injection site erythema	1 (3.33%)	1 (3.23%)	2 (3.28%)
Injection site induration	0 (0.00%)	1 (3.23%)	1 (1.64%)
Injection site pain	1 (3.33%)	0 (0.00%)	1 (1.64%)
Injection site pruritus	1 (3.33%)	0 (0.00%)	1 (1.64%)
Injection site reaction	2 (6.67%)	0 (0.00%)	2 (3.28%)
Oedema peripheral	2 (6.67%)	1 (3.23%)	3 (4.92%)
Hepatobiliary disorders			
Gallbladder polyp	2 (6.67%)	0 (0.00%)	2 (3.28%)
Liver disorder	0 (0.00%)	1 (3.23%)	1 (1.64%)
Immune system disorders			
Seasonal allergy	2 (6.67%)	0 (0.00%)	2 (3.28%)
Infections and infestations			
Bronchitis viral	0 (0.00%)	1 (3.23%)	1 (1.64%)
Cellulitis	0 (0.00%)	1 (3.23%)	1 (1.64%)
Conjunctivitis	1 (3.33%)	0 (0.00%)	1 (1.64%)

Coxsackie viral infection	0 (0.00%)	1 (3.23%)	1 (1.64%)
Gastroenteritis	3 (10.00%)	0 (0.00%)	3 (4.92%)
Gastroenteritis viral	1 (3.33%)	1 (3.23%)	2 (3.28%)
Hordeolum	0 (0.00%)	2 (6.45%)	2 (3.28%)
Lower respiratory tract infection	1 (3.33%)	0 (0.00%)	1 (1.64%)
Nasopharyngitis	0 (0.00%)	1 (3.23%)	1 (1.64%)
Oral herpes	1 (3.33%)	0 (0.00%)	1 (1.64%)
Sinusitis	2 (6.67%)	0 (0.00%)	2 (3.28%)
Tooth abscess	1 (3.33%)	0 (0.00%)	1 (1.64%)
Upper respiratory tract infection	5 (16.67%)	4 (12.90%)	9 (14.75%)
Urinary tract infection	0 (0.00%)	1 (3.23%)	1 (1.64%)
Viral infection	1 (3.33%)	1 (3.23%)	2 (3.28%)
Viral myositis	0 (0.00%)	1 (3.23%)	1 (1.64%)
Viral upper respiratory tract infection	0 (0.00%)	1 (3.23%)	1 (1.64%)
Injury, poisoning and procedural complications			

Cervical vertebral fracture	1 (3.33%)	0 (0.00%)	1 (1.64%)
Skin abrasion	0 (0.00%)	1 (3.23%)	1 (1.64%)
Investigations			
Blood pressure increased	0 (0.00%)	1 (3.23%)	1 (1.64%)
Weight decreased	1 (3.33%)	0 (0.00%)	1 (1.64%)
Metabolism and nutrition disorders			
Decreased appetite	5 (16.67%)	0 (0.00%)	5 (8.20%)
Increased appetite	3 (10.00%)	2 (6.45%)	5 (8.20%)
Iron deficiency	0 (0.00%)	1 (3.23%)	1 (1.64%)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (3.33%)	1 (3.23%)	2 (3.28%)
Back pain	3 (10.00%)	2 (6.45%)	5 (8.20%)
Intervertebral disc degeneration	1 (3.33%)	1 (3.23%)	2 (3.28%)
Limb discomfort	1 (3.33%)	0 (0.00%)	1 (1.64%)
Muscle oedema	0 (0.00%)	1 (3.23%)	1 (1.64%)
Musculoskeletal pain	1 (3.33%)	3 (9.68%)	4 (6.56%)

Myalgia	1 (3.33%)	0 (0.00%)	1 (1.64%)
Myosclerosis	0 (0.00%)	1 (3.23%)	1 (1.64%)
Pain in extremity	1 (3.33%)	1 (3.23%)	2 (3.28%)
Spinal osteoarthritis	1 (3.33%)	0 (0.00%)	1 (1.64%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma	0 (0.00%)	1 (3.23%)	1 (1.64%)
Skin papilloma	0 (0.00%)	1 (3.23%)	1 (1.64%)
Nervous system disorders			
Dizziness	0 (0.00%)	1 (3.23%)	1 (1.64%)
Dysgeusia	1 (3.33%)	0 (0.00%)	1 (1.64%)
Headache	1 (3.33%)	2 (6.45%)	3 (4.92%)
Migraine	1 (3.33%)	0 (0.00%)	1 (1.64%)
Neuropathy peripheral	1 (3.33%)	0 (0.00%)	1 (1.64%)
Paraesthesia	2 (6.67%)	0 (0.00%)	2 (3.28%)
Psychiatric disorders			
Anxiety	0 (0.00%)	1 (3.23%)	1 (1.64%)

Insomnia	1 (3.33%)	0 (0.00%)	1 (1.64%)
Renal and urinary disorders			
Nephrolithiasis	1 (3.33%)	0 (0.00%)	1 (1.64%)
Renal colic	1 (3.33%)	0 (0.00%)	1 (1.64%)
Renal cyst	3 (10.00%)	3 (9.68%)	6 (9.84%)
Reproductive system and breast disorders			
Uterine haemorrhage	0 (0.00%)	1 (3.23%)	1 (1.64%)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (3.33%)	0 (0.00%)	1 (1.64%)
Nasal congestion	0 (0.00%)	2 (6.45%)	2 (3.28%)
Sinus congestion	1 (3.33%)	1 (3.23%)	2 (3.28%)
Throat tightness	1 (3.33%)	0 (0.00%)	1 (1.64%)
Skin and subcutaneous tissue disorders			
Dermatitis contact	0 (0.00%)	1 (3.23%)	1 (1.64%)

Ecchymosis	1 (3.33%)	0 (0.00%)	1 (1.64%)
Rash	2 (6.67%)	1 (3.23%)	3 (4.92%)
Vascular disorders			
Hypertension	2 (6.67%)	0 (0.00%)	2 (3.28%)
Peripheral venous disease	0 (0.00%)	1 (3.23%)	1 (1.64%)

Conclusion:
LLF580 was generally safe and well tolerated at a repeated dose of 300 mg subcutaneously over 12 weeks in obese subjects.

Date of Clinical Study Report

20-July-2020