Sponsor

Novartis

Generic Drug Name

LFG316

Trial Indication

Neovascular Age Related Macular Degeneration (Neovascular AMD)

Protocol Number

CLFG316A2202

Protocol Title

A multicenter, randomized, sham-controlled, repeat-dose study to assess the safety, tolerability, serum pharmacokinetics, and efficacy of intravitreal LFG316 in patients with neovascular age-related macular degeneration

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

06-Feb-2012 to 25-Jul-2013

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a single-blind (patient), parallel assignment study in which patients with age-related macular degeneration were randomized in a 2:1 ratio to receive either intravitreal (IVT) LFG316 (5 mg/50 µL) or sham injection (placement of the syringe hub against the sclera, without use of a needle) to the study eye every four weeks for a total of three doses. The study consisted of up to 30-day screening period, a baseline visit, and a treatment period consisting of multiple outpatient visits, and an end-of-study visit.

Centers

Seven centers in the US

Publication

None

Objectives:

The primary objective was to evaluate the rate at which subjects required retreatment with anti-VEGF at three months. Secondary objectives included evaluation of the proportion of subjects in the study that requires at least one treatment of anti-Vascular Endothelial Growth Factor (anti-VEGF), the effect of three successive intravitreal doses of LFG316 on: visual acuity, central retinal thickness and choroidal neovascular membrane area, and drusen area/volume (where measurable). The serum concentrations of total LFG316 and total Complement Factor C5 (C5) during the course of the study were measured and the safety and tolerability of three successive IVT doses of LFG316 in subjects with neovascular AMD were evaluated.

Test Product, Dose, and Mode of Administration

LFG316 20 mg lyophilisate in vial; Intravitreal injection 5 mg/50 µL

Statistical Methods

A Bayesian analysis of the anti-VEGF retreatment rate was conducted and Bayesian posterior probabilities were calculated for LFG316 treated subjects compared to sham injection-treated subjects for three hypotheses of interest: 1) Minimal relevant effect, i.e., a minimal percent reduction in anti-VEGF retreatment rate of at least 35% in the LFG316 treated subjects; 2) No effect, i.e., the anti-VEGF retreatment rate in LFG316 group was no larger than that in sham

group; and 3) Very promising effect, i.e., a percent reduction in anti-VEGF retreatment rate of at least 75% in LFG316 treatment group.

The study was considered positive for efficacy if LFG316 had at least 95% probability of an reduction of ≥ 0% in anti-VEGF rate compared to sham; and, LFG316 had at least 50% probability of a reduction of 35% relative to sham.

Adverse events were summarized by the number and percentage of subjects who had any adverse event (AE), who had an AE in each body system, and who had each individual AE.

Study Population: Key Inclusion/Exclusion Criteria

Male and female patients with neovascular AMD, age 55 years to 90 years

Inclusion Criteria:

- Best corrected visual acuity (ETDRS scale) of 60 letters or less in the study eye.
- An active choroidal neovascular membrane attributable to neovascular AMD in at least one eye.
- History of treatment (at any time) with at least 3 doses of anti-VEGF therapy in the study eye.

Exclusion Criteria:

- History of recurrent non-response to anti-VEGF therapy in the study eye.
- In the study eye, retinal disease other than AMD (benign conditions of the vitreous and peripheral retina are not exclusionary).
- Choroidal neovascularization due to a cause other than AMD.
- In the study eye, media opacity that, in the investigator's opinion, could interfere with conduct of the study.
- History of infectious uveitis or endophthalmitis in either eye.
- Any of the following treatments to the study eye within 28 days prior to dosing: ranibizumab, bevacizumab, pegaptanib or other VEGF inhibitor.
- Any of the following within 90 days prior to dosing: photodynamic therapy or laser photocoagulation in the study eye; intravitreal steroid in the study eye; or intraocular surgery (including cataract surgery) in the study eye

Participant Flow Table

	LFG316 5mg/50µL IVT injection N = 30 n(%)	Sham injection N = 15 n(%)	Total N = 45 n(%)
Patients			
Completed	27 (90.0%)	14 (93.3%)	41 (91.1%)
Discontinued	3 (10.0%)	1 (6.7%)	4 (8.9%)
Administrative problems	1 (3.3%)	0 (0%)	1 (2.2%)
Lost to follow-up	1 (3.3%)	0 (0%)	1 (2.2%)
Subject withdrew consent	1 (3.3%)	1 (6.7%)	2 (4.4%)

Baseline Characteristics

		LFG316 5mg/50µL IVT injection N = 30	Sham injection N = 15	Total N = 45
Age (years)	Mean (SD)	79.7 (8.1)	78.8 (6.4)	79.4 (7.5)
	Median	82.0	79.0	80.0
	Range	59 - 89	62 - 88	59 - 89
Gender – n (%)	Male	11 (37%)	8 (53%)	19 (42%)
	Female	19 (63%)	7 (47%)	26 (58%)
Predominant race - n(%)	Caucasian	30 (100%)	13 (87%)	43 (96%)
	Other	0 (0%)	2 (13%)	2 (4%)
Ethnicity - n(%)	Hispanic/Latino	6 (20%)	4 (27%)	10 (22%)
	Mixed Ethnicity	1 (3%)	0 (0%)	1 (2%)
	Other	23 (77%)	11 (73%)	34 (76%)
Height (cm)	Mean (SD)	163.7 (9.8)	165.8 (11.8)	164.4 (10.4)
	Median	162.0	165.1	162.6
	Range	145 - 184	142 - 185	142 - 185
Weight (kg)	Mean (SD)	76.8 (17.9)	79.6 (14.3)	77.7 (16.7)
	Median	74.8	80.3	76.7
	Range	48 - 113	45 - 102	45 - 113
BMI (kg/m2)	Mean (SD)	28.6 (5.9)	29.0 (5.0)	28.7 (5.6)
	Median	27.5	28.5	28.0
	Range	21 - 44	18 - 39	18 - 44

Summary of Efficacy

Primary Outcome Results

Bayesian analysis of anti-VEGF retreatment rate at 3 months (Day 85) (Pharmacodynamic analysis set)

		Posterior _Credibility Interval_	
Treatment effect / contrast	**Mean**	**0.025**	**0.975**
RR_LFG316	0.094	0.064	0.129
RR_Sham	0.081	0.044	0.128
Ratio (RR_LFG316/ RR_Sham)	1.246	0.640	2.284
Probability RR_LFG316 / RR_Sham < 1 | data	0.305		
Probability RR_LFG316 / RR_Sham < 0.65 | data	0.028		
Probability RR_LFG316 / RR_Sham < 0.25 | data	0.000		

RR: Retreatment Rate (expressed in nb/week)
* Probability { RR_LF316 / RR_Sham < 1 | data }>=95%
**Probability { RR_LF316 /RR_Sham < 0.65 | data }>=50%
First criteria based on minimal % reduction in anti-VEGF RR of at least 35% under LFG316 relative to sham; Second criteria based on targeting a % reduction in anti-VEGF RR of at least 75% under LFG316 relative to sham .

Secondary Outcome Results

Summary of visual acuity over time – ETDRS score (unit: letter) – study eye (Pharmacodynamic analysis set)

		LFG316 5mg/50µL IVT injection N = 29	Sham injection N = 15
Study Day			
SCR	Mean	39.8	35.9
	SD	18.24	18.89
	Median	36.0	35.0
	Range	2 - 69	8 - 59

Study Day		LFG316 5mg/50µL IVT injection N = 29	Sham injection N = 15
Baseline D1	Mean	40.6	36.7
	SD	17.48	19.23
	Median	43.0	39.0
	Range	3 - 74	4 - 62
Day 2	Mean	40.7 [0.1]	36.4 [-0.3]
	SD	17.78 [3.19]	17.80 [4.97]
	Median	41.0 [0.0]	38.0 [-1.0]
	Range	3 - 77 [-4 - 9]	6 - 61 [-7 - 15]
Day 15	Mean	43.0 [2.0]	42.0 [4.0]
	SD	18.35 [7.26]	20.66 [13.01]
	Median	45.0 [2.5]	45.0 [1.0]
	Range	5 - 74 [-22 - 20]	7 - 76 [-7 - 47]
Day 29	Mean	44.5 [3.6]	39.4 [3.7]
	SD	18.11 [6.17]	20.50 [8.24]
	Median	46.0 [3.0]	44.0 [3.0]
	Range	5 - 73 [-7 - 18]	8 - 67 [-4 - 29]
Day 43	Mean	43.4 [2.0]	36.7 [-0.1]
	SD	17.70 [8.36]	19.19 [3.95]
	Median	45.0 [1.0]	37.0 [-1.0]
	Range	7 - 70 [-19 - 17]	8 - 62 [-5 - 8]
Day 57	Mean	42.5 [2.1]	37.8 [1.1]
	SD	18.71 [7.51]	20.76 [5.48]
	Median	45.0 [2.0]	42.0 [1.0]
	Range	9 - 74 [-14 - 24]	7 - 66 [-8 - 13]
Day 71	Mean	45.7 [4.3]	40.5 [2.6]
	SD	16.34 [8.20]	20.06 [5.71]

Study Day		LFG316 5mg/50µL IVT injection N = 29	Sham injection N = 15
	Median	48.0 [2.0]	42.5 [2.5]
	Range	10 - 74 [-17 - 24]	6 - 71 [-5 - 11]
Day 85	Mean	45.4 [3.2]	39.5 [1.6]
	SD	17.39 [8.27]	20.05 [6.66]
	Median	48.5 [2.0]	38.5 [2.0]
	Range	5 - 74 [-15 - 24]	7 - 67 [-10 - 14]
Day 113	Mean	41.8 [1.5]	39.9 [3.2]
	SD	17.83 [8.37]	20.40 [7.12]
	Median	41.0 [2.0]	35.0 [4.0]
	Range	6 - 73 [-16 - 23]	8 - 68 [-11 - 13]

Summary of central retinal thickness (µm) over time – study eye (Pharmacodynamic analysis set)

Study Day		LFG316 5mg/50µL IVT injection N = 29	Sham injection N = 15
Baseline D1	Mean	360.1	392.7
	SD	216.71	389.68
	Median	290.5	237.0
	Range	50 - 925	112 - 1523
Day 85	Mean	341.5 [-24.1]	318.3 [-61.8]
	SD	225.66 [193.58]	233.37 [390.26]
	Median	275.0 [-20.0]	296.0 [-34.0]
	Range	15 - 1133 [-474 - 355]	71 - 936 [-1115 - 617]

Values in [ ] indicate change from baseline (Day1 predose).

Summary of neovascular membrane area (mm^2) over time – study eye (Pharmacodynamic analysis set)

		LFG316 5mg/50µL IVT injection N = 29	Sham injection N = 15
Study Day			
SCR	Mean	7.5	6.1
	SD	8.45	9.85
	Median	5.5	1.2
	Range	0 - 28	0 - 31
Day 85	Mean	6.1 [-2.1]	4.5 [-2.1]
	SD	9.48 [6.60]	8.05 [3.83]
	Median	2.7 [-1.5]	0.0 [0.0]
	Range	0 - 43 [-19 - 13]	0 - 24 [-12 - 1]

Values in [ ] indicate change from baseline (Screening).

Change from baseline to Day 85 in drusen area – total area – study eye (Pharmacodynamic analysis set)

	LFG316 5mg/50µL IVT injection N = 29	Sham injection N = 14
Drusen area		
No Change	4 (13.8%)	2 (14.3%)
Worsen †	1 (3.4%)	
Not assessable / Unreadable	24 (82.8%)	12 (85.7%)

†: Worsen = increase of one category or more from baseline; ‡: Improved = decrease of one category or more from baseline. Not assessable if not assessed at baseline or on Day 85

Summary of Safety

Safety Results

Non-Ocular Adverse Events by System Organ Class

	LFG316 N = 30 n (%)	Sham N = 15 n (%)	Total N = 45 n (%)
Patients with AE(s)	16 (53.3%)	9 (60.0%)	25 (55.6%)
Infections and infestations	6 (20.0%)	4 (26.7%)	10 (22.2%)
Injury, poisoning and procedural complications	5 (16.7%)	1 (6.7%)	6 (13.3%)
Gastrointestinal disorders	3 (10.0%)	3 (20.0%)	6 (13.3%)
Vascular disorders	2 (6.7%)	3 (20.0%)	5 (11.1%)
Investigations	3 (10.0%)	2 (13.3%)	5 (11.1%)
Nervous system disorders	3 (10.0%)	1 (6.7%)	4 (8.9%)
Musculoskeletal and connective tissue disorders	2 (6.7%)	2 (13.3%)	4 (8.9%)
Metabolism and nutrition disorders	2 (6.7%)	1 (6.7%)	3 (6.7%)
Immune system disorders	2 (6.7%)	1 (6.7%)	3 (6.7%)
General disorders and administration site conditions	2 (6.7%)	1 (6.7%)	3 (6.7%)
Cardiac disorders	1 (3.3%)	2 (13.3%)	3 (6.7%)

Non-Ocular Adverse Events by Preferred Term

	LFG316 N = 30 n (%)	Sham N = 15 n (%)	Total N = 45 n (%)
Patients with AE(s)	16 (53.3%)	9 (60.0%)	25 (55.6%)
Upper respiratory tract infection	2 (6.7%)	1 (6.7%)	3 (6.7%)
Muscle strain	2 (6.7%)	1 (6.7%)	3 (6.7%)
Hypertension	1 (3.3%)	2 (13.3%)	3 (6.7%)
Gastrooesophageal reflux disease	2 (6.7%)	1 (6.7%)	3 (6.7%)
Dizziness	2 (6.7%)	1 (6.7%)	3 (6.7%)

Ocular Adverse Events in the study eye by preferred term

	LFG316 N = 30 n (%)	Sham N = 15 n (%)	Total N = 45 n (%)
Patients with AE(s)	10 (33.3%)	4 (26.7%)	14 (31.1%)
Conjunctival haemorrhage	6 (20.0%)	1 (6.7%)	7 (15.6%)

Serious Adverse Events

	LFG316 N = 30 n (%)	Sham N = 15 n (%)
No. (%) of subjects studied	30	15
No. (%) of subjects with AE(s)	16 (53.3%)	9 (60.0%)
Number (%) of subjects with serious or other significant events	n (%)	n (%)
SAE(s)	1 (0.1)	2 (0.0)
Discontinued due to SAE(s)	0 (3.3)	0 (13.3)

Other Relevant Findings

After intravitreal administration,LFG316 distributed from the eye into the blood where it was detected as total LFG316. LFG316 could be detected in the majority of samples collected at 7 or 14 days post dose and in approximately 40% of subjects at 28 days post dose. At the end of study (approximately 8 weeks after the administration of the last dose), total LFG316 was not detected in any sample collected. The highest observed concentration was 1.49 µg/mL and was observed on Study Day 43 (14 days after the administration of the second dose of LFG316).

After the first dose, the mean concentration of total LFG316 was similar on Day 8 and 15, being 0.370 and 0.375 µg/mL,respectively. The mean concentration of total LFG316 at 14 days after the administration of the first, second and third dose was similar, being 0.375, 0.383 and 0.409 µg/mL, respectively. At 28 days after the administration of the first, second or third doses, the mean concentration of total LFG316 was 0.124, 0.156 and 0.160 µg/mL, respectively. The mean concentration at 28 days post dose was below the limit of quantification.

Prior to the administration of the first dose of LFG316, the mean concentration of C5 were similar for subjects that were subsequently dosed with LFG316 or administered a sham injection, with the mean concentration being 163.62 and 154.73 µg/mL. The serum concentrations of total C5 were broadly similar at all post-dose time points, with no discernable pattern that could be attributed to the administration of LFG316. Similarly, the serum concentrations of total C5 were similar at all time points in the subjects that were administered a sham injection. There was no marked difference in serum total C5 concentrations between the LFG316 dosed or sham dosed subjects

Conclusion:

Monthly LFG316 5 mg IVT treatment was well tolerated with a similar safety profile observed in both the LFG316 treated and sham groups.

With respect to primary efficacy parameters, no significant difference between LFG316 and sham treatment in anti-VEGF retreatment rate and use was observed.

Similarly, no significant difference between LFG316 and sham treatment was observed in any of the secondary efficacy parameters: visual acuity, central retinal thickness, choroidal neovascular membrane area. However, patients who

received LFG316 treatments but did not receive any anti-VEGF retreatments showed statistically significant improvement in visual acuity [7.20 (95% CI: -0.02, 14.41, p-value = 0.05) letters at Day 43 and a marginally significant difference of 7.34 (95% CI: -0.25, 14.93, p-value = 0.06) letters at Day 71] as compared to sham treated patients who did not receive any anti-VEGF retreatments

After intravitreal administration, LFG316 distributed from the eye into the systemic circulation and was then slowly cleared from the serum. LFG316 could be detected in the majority of samples collected at 7 or 14 days post dose and in approximately 40% of subjects at 28 days post dose. The highest observed concentration was 1.49 µg/mL.

The mean pre-study serum concentration of total C5 was similar for subjects in the LFG316 and sham groups (163.62 and 154.73 µg/mL, respectively). There was no evidence of an impact of the administration of LFG316 on the serum concentrations of total C5, consistent with the serum concentrations of total LFG316 being approximately 100-fold lower than the serum concentrations of C5.

Anti-LFG316 antibodies were not detected in any subject. Therefore, the lack of efficacy cannot be attributed to the presence of LFG316 antibodies.

Overall, monthly intravitreal injection of LFG316 was safe and tolerable but no efficacy was observed in reduction of the need for monthly anti-VEGF treatment.

Date of Clinical Trial Report

8 Jul 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

16 JULY 2014

Date of Latest Update

Reason for Update