Sponsor

Novartis

Generic Drug Name

LFG316

Therapeutic Area of Trial

Neovascular age-related macular degeneration

Approved Indication

Investigational

Protocol Number

CLFG316A2201

Title

A multiple dose, two-cohort study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of intravenous LFG316 in patients with neovascular age-related macular degeneration

Study Phase

Phase 2

Study Start/End Dates

First patient enrolled: 26-Dec-2012 to 13 May 2013

This study was initiated on 26 December 2012, but recruitment was stopped on 26 March 2013 after just four subjects had ben randomized. Novartis decision to terminate the CLFG316A2201 study was not due to any safety signal with LFG316. Intra venous infusion of LFG316 was safe and well tolerated and was note associated with any infections. However, systemic therapy with another anti-C5 antibody, Soliris® (Eculizumab) has been associated with the risk of meningococcal infection and unclear risk of death after multiple dosing, in some cases despite the vaccination. Thus Novartis decided that with current uncertain knowledge the risk/benefit ratio of treating patients with age related macular degeneration using systemic anti-C5 therapy was not favorable and stopped the study.

Study Design/Methodology

This was intended as a multiple dose, randomized, double-masked study to be conducted in multiple retina specialty clinics in the US and Europe. Patients were to be enrolled into one of two cohorts. Cohort 1 was planned to consist of 4 - 8 patients. Cohort 2 was to consist of 39 - 51 patients. For each cohort, the study would consist of a 45-day screening period, an approximately 85-day treatment period consisting of multiple outpatient visits, and an end-of-study visit. Study drug was to be administered intravenously 4 times (Cohort 1) or 3 times (Cohort 2). The study was terminated after just four subjects were enrolled in Cohort 1. No subjects were enrolled in Cohort 2.

Centers

Two centers in the US enrolled two subjects each.

Publication

None

Objectives

The two co-primary objectives were to evaluate the effect of successive IV doses of LFG316 on anti-VEGF retreatment rate and the safety and tolerability of successive IV doses of LFG316 in patients with AMD.

The secondary objectives were to evaluate the effect of successive IV doses of LFG316 on: visual acuity; central retinal thickness and choroidal neovascular membrane area; drusen volume, where measurable; and, serum total LFG316 levels and the pharmacodynamic profile in patients with neovascular AMD.

Test Product, Doses, and Mode of Administration

The investigational drug, LFG316 100 mg vials of lyophilized powder for reconstitution and intravenous infusion, were manufactured and packaged by Novartis and supplied to the investigator as open labeled bulk medication.

Sterile water for infusion (for LFG316 reconstitution) and Dextrose 5% in Water (D5W; for infusion) 250 mL i.v. bags were provided by the study clinic.

Placebo infusions contained D5W only.

Statistical Methods

Following the early termination of the study only the safety data set was analyzed. All patients who received study drug (who at least began infusion) were included in the safety analysis set. All safety data are provided.

Because the study was terminated prior to completion of enrolment no statistical analysis was performed and inferential and descriptive analyses were not provided. Nevertheless listings were provided for the data that were obtained for the four subjects enrolled.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Active choroidal neovascular AMD in at least one eye.

Exclusion Criteria:

- Retinal disease other than AMD that, in the investigator's opinion, would interfere with safety or study conduct.
- Choroidal neovascularization due to a cause other than AMD.
- In the study eye, media opacity that, in the investigator's opinion, would interfere with study conduct.
- Any disease or concomitant (or recent) medication expected to cause systemic immunosuppression.

- History of meningococcal meningitis in the past 10 years, or any history of recurrent meningitis.
- History of hospitalization for pneumococcal pneumonia within the past 3 years.
- History of serious systemic infection within the past 12 months.
- Any of the following treatments to the study eye within 7 days prior to study drug dosing: ranibizumab (Lucentis), bevacizumab (Avastin), pegaptanib (Macugen), or other VEGF inhibitors.

Participant Flow

	LFG316 N = 4
Patients	
Discontinued	4 (100.0%)
Administrative reasons	4 (100.0%)

Baseline Characteristics

		LFG316 N = 4
Age (years)	Mean (SD)	70.3 (9.3)
	Median	69.0
	Range	61 - 82
Gender - n(%)	Male	2 (50%)
	Female	2 (50%)
Predominant race - n(%)	Caucasian	4 (100%)
Ethnicity - n(%)	Other	4 (100%)
Height (cm)	Mean (SD)	176.5 (10.5)
	Median	179.0
	Range	162 - 186
Weight (kg)	Mean (SD)	92.6 (15.4)
	Median	92.6
	Range	75 - 110
BMI (kg/m2)	Mean (SD)	29.6 (2.5)
	Median	28.7
	Range	28 - 33

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Outcome Measures

Sumary of Efficacy

Primary Outcome Results:

No formal efficacy, pharmacokinetic or pharmacodynamic analyses were performed.

- Number of anti-vascular endothelial growth factor (anti-VEGF) retreatment vs time from Day 1 to Day 113 (Day 49 due to early termination).
  Due to early termination and number of enrolled patients in this study, no formal efficacy analysis was performed.

- Number and percentage of patients with adverse events from baseline to Day 113 (Day 49 due to early termination)
  Please see under “Safety Results” below.

Secondary Outcome Measures:

- Change in visual acuity from Day 1 to Day 113 (Day 49 due to early termination)
  Due to early termination and number of enrolled patients in this study, no formal analysis was performed

- Change in central retinal thickness, choroidal neovascular membrane area and drusen volume from Day 1 to Day 113 (day 49 due to early termination)
  Due to early termination and number of enrolled patients in this study, no formal analysis was performed

- Serum concentrations of total LFG316 versus time (Days 1, 8, 15, 22, 29, 43, 57, 78, 85 and 113).
  Pharmacokinetic endpoint was not analyzed due to early termination of the study and the small number of patients.

- Serum concentration of pharmacodynamic parameters (Wieslab and C5) versus time, (screening and Days 1, 8, 15, 22, 29, 43, 57, 78, 85 and 113)
  Pharmacodynamic endpoint was not analyzed due to early termination of the study and the small number of patients.

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Summary of Safety

Safety Results

Adverse Events by System Organ Class

	LFG316 N = 4 n (%)
Patients with at least one AE	4 (100)
Primary system organ class	
Blood & lymphatic system disorders	1 (25)
Eye disorders	2 (50)
Infections & infestations	1 (25)
Metabolism & nutrition disorders	1 (25)
Respiratory, thoracic & mediastinal disorders	1 (25)

Under one treatment, a subject with multiple occurrences of an AE is counted only once in the AE category. A subject with multiple adverse events within a body system is counted only once in the total row. N = number of subjects studied; n = number of subjects with at least one AE on the category. Only adverse events occurring at or after first drug intake are included.

Most Frequently Reported AEs Overall by preferred term (at least 1% incidence)

	LFG316 N = 4 n (%)
Patients with at least one AE	4 (100)
Anaemia	1 (25)
Eye pain	1 (25)
Lacrimation increased	1 (25)
Photophobia	1 (25)
Visual acuity reduced	1 (25)
Vitreous detachment	1 (25)
Vitreous floaters	1 (25)
Otitis media	1 (25)
Diabetes mellitus	1 (25)
Chronic obstructive pulmonary disease	1 (25)
Dyspnoea	1 (25)

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Serious Adverse Events and Deaths

	LFG316
No. (%) of subjects studied	4 (100)
No. (%) of subjects with AE(s)	4 (100)
Number (%) of subjects with serious or other significant events	1 (25)
Death	0 (0)
SAE(s)	1 (25)
Discontinued due to SAE(s)	0 (0)

Conclusion

Intravenous administration of LFG316 was safe and well tolerated without any drug related adverse events. Intravenous LFG316 resulted in a marked suppression of serum complement activity, consistent with its proposed mechanism of action, in all patients. It was noted that the duration of suppression of serum complement activity was shorter for Subject 1004/5101 compared to the other subjects, consistent with the lower concentrations of total LFG316 in this subject compared to the other subjects. Anti-LFG316 antibodies were not detected in this study.
The U.S. Food and Drug Administration (FDA) has approved the use of Solaris® (eculizumab), which also inhibits the activation of C5,for treatment of pediatric and adult patients with atypical hemolytic uremic syndrome and the treatment of patients with paroxysmal nocturnal hemoglobinuria. However, treatment with eculizumab is associated with life-threatening and fatal meningococcal infections and the product labeling contains a warning to inform healthcare providers and patients of the serious risk of meningococcal infection despite vaccination. Consequently, Novartis took the decision to stop the CLFG316A2201 study due to potential risk of meningococcal infection and unclear risk of death noted after multiple dosing with Soliris® (eculizumab). There was no finding with LFG316 to indicate that LFG316 presented any risk to patients.

Date of Clinical Trial Report

28 Apr 2014

Date Inclusion on Novartis Clinical Trial Results Database

29 April 2014