CLINICAL STUDY REPORT

TITLE:	**A PHASE Ib/II, MULTICENTER, RANDOMIZED, SINGLE-MASKED, SHAM INJECTION–CONTROLLED STUDY OF SAFETY, TOLERABILITY, AND EVIDENCE OF ACTIVITY OF FCFD4514S INTRAVITREAL INJECTIONS ADMINISTERED MONTHLY OR EVERY OTHER MONTH TO PATIENTS WITH GEOGRAPHIC ATROPHY**
STUDY DRUG:	Lampalizumab (FCFD4514S)
INDICATION:	Geographic Atrophy
REPORT NUMBER:	CSR CFD4870g
EUDRACT NUMBER:	2010-019183-36
IND:	BB-IND 104996
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
SPONSOR'S MEDICAL OFFICER:	[redacted]
SPONSOR'S SIGNATORY:	[redacted]
REPORT PREPARED BY:	[redacted]
RECORDS RETENTION:	Genentech Central Records
STUDY DATES:	Initiation: 18 November 2010 Completion: 22 April 2013
REPORT DATE:	12 March 2014

SYNOPSIS OF CLINICAL STUDY REPORT

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Title of Study:	A Phase Ib/II, Multicenter, Randomized, Single-Masked, Sham Injection–Controlled Study of Safety, Tolerability, and Evidence of Activity of FCFD4514s Intravitreal Injections Administered Monthly or Every Other Month to Patients with Geographic Atrophy
Phase of Development:	Ib/II
Investigators:	6 investigators in Germany; 26 investigators in the United States
Study Centers:	Safety Run-In (Phase Ib): 7 sites in the United States Randomized (Phase II): 6 sites in Germany and 26 sites in the United States
Publications:	No publications have resulted from this study.
Study Period:	18 November 2010 to 22 April 2013

Objectives

Primary:

- To evaluate the ocular and systemic safety and tolerability of lampalizumab administered intravitreally (ITV) monthly or every other month
- To investigate evidence of activity with an anatomic outcome of lampalizumab administered ITV monthly or every other month compared with sham control

Secondary:

- To assess best corrected visual acuity (BCVA) on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart at starting distance of 4 meters following ITV lampalizumab administered monthly or every other month compared with sham control
- To characterize systemic immunogenicity of lampalizumab following multiple ITV doses of lampalizumab
- To characterize the serum pharmacokinetics (PK) of lampalizumab following multiple ITV doses of lampalizumab

Exploratory:

- To assess mean change in drusen volume following multiple ITV doses of lampalizumab
- To evaluate the conversion rate to wet age-related macular degeneration (AMD) in study eyes treated with lampalizumab versus sham control
- To assess visual function measures following ITV doses of lampalizumab administered monthly or every other month compared with sham
- To evaluate the relationship between specific genetic polymorphisms associated with AMD, disease characteristics, and response to lampalizumab

Methodology

Study CFD4870g included a Phase Ib safety run-in component that preceded the randomized Phase II study. The Phase Ib run-in assessment evaluated the safety and tolerability of multiple monthly administrations of 10 mg of lampalizumab ITV. The Phase II portion of the study was a multicenter, randomized, single-masked, sham injection–controlled study of safety, tolerability, and evidence of activity of lampalizumab ITV injections administered monthly or every other month for an 18-month treatment period in patients with geographic atrophy (GA). Primary, secondary, and exploratory outcomes were assessed at the conclusion of the 18-month treatment period.

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Patients who did not qualify or chose not to continue in the open-label extension study (OLE, Study GX28198) continued in Study CFD4870g for a 3-month safety follow-up period after their final dose of study drug or sham injection. Patients in the every-other-month treatment arms had safety visits at Months 17, 18, and 19; patients in the monthly treatment arms had safety visits at Months 18, 19, and 20. Patients who continued into the OLE study had their final safety visit at Month 18. Site investigators were qualified ophthalmologists. The Phase Ib safety run-in assessment was conducted in the United States; the randomized Phase II portion of the study was conducted in the United States and Germany. The Phase Ib/II study was designed to enroll approximately 135 patients with GA secondary to AMD.

Number of Patients (Planned and Analyzed):

Planned: Approximately 120 patients with GA secondary to AMD in both eyes
Analyzed: A total of 129 patients were randomized to the Phase II portion of the study.

Diagnosis and Main Criteria for Inclusion:

The Phase Ib/II study was designed to enroll approximately 135 patients with GA secondary to AMD. Patient selection criteria were the same for both the safety run-in phase and randomization phase, with the exception of ocular inclusion criteria; patients with less severe visual impairment were enrolled in the randomized phase of the study.

Eligible patients were aged 60–89 years with a well-demarcated area of GA secondary to AMD in the absence of choroidal neovascularization (CNV). All study eyes had BCVA Snellen equivalent between 20/50 and 20/400 inclusive (between 20/125 and 20/400 for the Phase Ib portion), banded or diffuse hyperautofluorescence adjacent to the GA lesion on fundus autofluorescence (FAF), and a GA lesion measuring between ≥ 1 disc area (DA, 2.5 mm^2) and ≤ 7 DA (17.5 mm^2). For patients with multifocal GA, ≥ 1 focal lesion was required to measure ≥ 0.5 DA (1.25 mm^2). Select exclusion criteria included previous ITV therapy, retina surgery, or other therapeutic procedures in the study eye, GA in either eye due to causes other than AMD, subfoveal focal laser photocoagulation in the study eye, and select concurrent ocular and systemic conditions.

Test Product, Dose and Mode of Administration, Batch Number:

10 mg lampalizumab for ITV injection monthly or every other month

Lot Numbers: [redacted]

Duration of Treatment:

Safety Run-In Phase: Lampalizumab was administered monthly every 30 (± 7) days until the 10th evaluable patient completed the Day 90 (± 7) visit following the third lampalizumab treatment, followed by a dosing hiatus of approximately 7 days. Following the hiatus, patients continued monthly study drug administration at the same dose as the patients in the randomized phase for the remainder of their 18-month treatment period, adhering to the same visit frequency as the randomized phase monthly dosing arm.

Randomized Phase: Lampalizumab was administered monthly or every other month for a total of 18 injections in the monthly treatment group and a total of 9 injections in the every-other-month treatment group.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Randomized Phase: Sham injections were administered monthly or every other month

Lot Numbers: [redacted]

Criteria for Evaluation

Efficacy:

The efficacy analyses were based on a modified intent-to-treat (mITT) population, including all randomized patients who received at least one dose of treatment and had at least one

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post-baseline primary efficacy measurement. Treatment groups for this population were defined according to the treatment assignment at randomization. Patients in the sham monthly and sham every-other-month groups were pooled. Unless otherwise specified, analyses were performed with missing data imputed using the last observation carried forward (LOCF) method and with observed data (i.e., no imputation for missing data) for primary and secondary endpoints; for exploratory endpoints and exploratory analyses of the primary endpoints (e.g., subgroup analysis by biomarker status), analyses were performed with the observed data.

Safety:

The safety-evaluable analysis population included patients who received at least one dose of study drug in the Phase II portion of this study. Treatment groups for this population were defined according to the actual treatment received during the 18-month treatment period, as follows: the treatment frequency group (monthly or every other month) for each patient was as randomized; if a patient received only one type of treatment (10 mg lampalizumab or sham), the patient's treatment group was that of the treatment received; and if a patient received a combination of different treatments (10 mg lampalizumab or sham), the patient's treatment group was based on the treatment of the majority of the treatment given.

For all treatment patients, the treatment group in the safety-evaluable population was the same as the treatment group assigned at the randomization.

Pharmacokinetics/Pharmacodynamics:

The PK-evaluable patients, defined by availability of serum samples and treatment actually received, was the patient population used for the PK analyses.

Statistical Methods

All tests were performed at the significance level of 0.05 and there was no multiplicity adjustment.

Primary Endpoint:

The primary efficacy endpoint was mean GA area growth rate from baseline to Month 18 as measured by FAF; the primary efficacy endpoint was analyzed at Month 18. Stratified analysis of variance (ANOVA) was used for the primary analysis with baseline lesion size as the stratification variable.

Secondary Endpoint:

Analysis methods similar to those of the primary endpoint were used for secondary endpoints of mean growth rate of GA area from baseline to Month 18 as assessed by digitized stereoscopic color fundus photographs (CFPs) and mean change in BCVA from baseline to Month 18 with use of the ETDRS system. The mean change in BCVA from baseline to Month 18 was analyzed using the analysis of covariance (ANCOVA) model adjusted for baseline BCVA score and baseline GA lesion size category.

Pharmacokinetics/Pharmacodynamics:

Individual and mean serum lampalizumab concentration–time data were tabulated and plotted by dose level. The serum PK of lampalizumab were summarized by parameter estimates of exposure between dose intervals (AUC), maximum observed serum concentration (C_{max}), and time to steady-state and accumulation ratio (AR). Estimates for these parameters were tabulated and summarized by descriptive statistics. Anterior chamber (aqueous humor) paracentesis samples were collected at select U.S. sites to assess PK and pharmacodynamics (PD) relationships. Additional PK, PD, and biomarker investigations were conducted as appropriate.

Summary of Results and Conclusions

Efficacy Conclusions:

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- The primary efficacy endpoint is derived as the mean change in GA area from baseline to Month 18 as measured by FAF. The pre-specified primary analysis (mITT with LOCF method) showed that the CFD4870g Phase II study met its primary endpoint and met its secondary endpoint of mean change in GA area from baseline to Month 18 as assessed by CFPs in the lampalizumab monthly group. A positive treatment effect in slowing GA area growth was observed in the monthly group by 6 months and extending through 18 months. The results demonstrated a statistically significant benefit of lampalizumab administered monthly on reducing GA area growth over the 18-month study-treatment period in all mITT patients. The robustness of the results of the primary endpoint was demonstrated by consistent results from various sensitivity analyses.
- The pre-specified analysis of BCVA endpoints (mITT with LOCF method) showed that no clinical benefit was observed in the BCVA secondary endpoint.
- In the primary analysis, all mITT patients treated with monthly lampalizumab had slower GA growth compared with patients treated with sham; the mean difference in GA growth at Month 18 was 0.595 mm^2 (80% CI: 0.109, 1.081; $p = 0.1170$), corresponding to a reduction rate in GA of 20.4% (80% CI: 4%, 37%). The reduction rate is calculated as $100\% \times$ [(mean change in sham pooled − mean change in lampalizumab group)/mean change in sham pooled]. In an exploratory analysis of genetic biomarkers, greater efficacy was observed in the subgroup of biomarker-positive patients compared with the biomarker-negative patients. In biomarker-positive patients, there was a 44% reduction (~80% CI: 25%, 63%; $p = 0.0037$) at Month 18 in the lampalizumab monthly group and an 18% reduction (~80% CI: −1%, 36%; $p = 0.2266$) at Month 18 in the lampalizumab every-other-month group; these results suggest a potential dose-response relationship. There was no apparent lampalizumab treatment response in either monthly or every-other-month biomarker-negative patients. These results also suggest that the biomarker appears to be both prognostic for GA progression and predictive for lampalizumab treatment response. Approximately 76% of all mITT patients (93 of 123) were assayed and 57% of assayed patients were biomarker positive. In patients whose samples were not available, no apparent treatment effect was observed in both lampalizumab treatment groups with the mean change in GA growth from baseline to Month 18 of 2.050 mm^2 in the pooled sham group, 2.432 mm^2 in the lampalizumab monthly group, and 3.763 mm^2 in the lampalizumab every-other-month group, respectively.

Pharmacodynamic/Pharmacokinetic Conclusions:

- Serum lampalizumab concentrations at all observed timepoints in all lampalizumab-treated patients (maximum 476 ng/mL) were below the minimal concentration (2000 ng/mL) that produced transient systemic inhibition of alternative complement pathway activity in a cynomolgus monkey model.
- Minimum serum lampalizumab concentrations (C_{min}) appeared to reach steady state after the first dose for both monthly (at Month 1) and every-other-month (at Month 2) groups.
- No accumulation in serum lampalizumab concentrations was observed on the basis of geometric means of the C_{min}-based ARs for both monthly and every-other-month groups.
- The majority of samples of trough concentrations in the monthly dosing group ($> 87.1\%$) were above the lower limit of quantification (LLOQ = 0.35 ng/mL), whereas the majority of samples of trough concentrations in the every-other-month dosing group ($> 56.4\%$) were below LLOQ.
- Geometric means of trough concentrations ranged from 6.9–11.9 ng/mL at 30 days after dosing in the monthly dosing group and was significantly higher than those in the every-other-month dosing group (1.1–1.2 ng/mL at 60 days after dosing).

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Safety Conclusions:

- Overall, 10-mg injections of lampalizumab monthly or every other month showed acceptable safety and tolerability in patients with GA secondary to AMD.
- In the Phase Ib portion of the study, there was one death due to cardiac arrest; this event was not attributed to study drug.
- No pregnancies were reported.
- No lampalizumab-related ocular serious adverse events (SAEs) occurred. No patients were discontinued from lampalizumab treatment because of an SAE in the study eye.
- No lampalizumab-related non-ocular SAEs occurred.
- No endophthalmitis was reported.
- The most frequent ocular adverse events (AEs) reported in the study eye were conjunctival hemorrhage (34.9%), eye pain (15.5%), and increased intraocular pressure (IOP; 10.1%); the most common AE in the fellow eye was cataract (9.1%).
- A total of 7 patients had non-serious ocular AEs suspected to be related to study drug; these included visual impairment, vitritis, increased IOP, vitreous opacities, CNV, and anterior chamber inflammation.
- Intraocular inflammation and IOP elevation rates were consistent with the Sponsor's experience with ranibizumab treatment in wet (neovascular) AMD.
- The most frequent non-ocular (systemic) AEs were hypertension (11%), nasopharyngitis (10.5%), and urinary tract infection (10%). The majority of the non-ocular AEs were mild or moderate in severity. Three non-serious, non-ocular (systemic) AEs were reported to be related to lampalizumab in 2 patients (one each in the lampalizumab monthly and every-other-month groups): alanine aminotransferase increase (1), aspartate aminotransferase increase (1), and complement factor decrease (1).
- The most frequent non-ocular (systemic) SAEs were aortic stenosis (2), coronary artery disease (2), gastrointestinal hemorrhage (2), myocardial infarction (2), pneumonia (2), prostate cancer (2), and rectal hemorrhage (2).
- There were 5 Phase II patients treated with lampalizumab who were discontinued from study treatment because of non-ocular (systemic) AEs; 2 treatment discontinuations were the result of non-serious AEs (basal cell carcinoma and prostate cancer), and 3 treatment discontinuations resulted from SAEs of cardiac arrest, prostate cancer, and dementia of Alzheimer's type. All 5 non-ocular (systemic) treatment discontinuations were reported as unrelated to lampalizumab.
- Laboratory test results from blood chemistry, hematology, and urinalysis; vital signs; and physical examination findings did not identify any patterns of lampalizumab-related effects. There were no adverse changes observed in systemic complement activity analyzed by AH50 (alternative complement pathway) and CH50 (classical complement pathway) assays with one exception. A single AE was reported for depression of CH50 that was suspected to be related to lampalizumab.
- The treatment-emergent anti-therapeutic antibody (ATA) rate was 7.0% in the lampalizumab monthly group and 11.9% in the lampalizumab every-other-month group. The observed immunogenicity rates for lampalizumab were consistent with reported rates for ranibizumab in neovascular (wet) AMD studies, and there was no ATA effect on PK, safety, or efficacy.

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Overall Conclusions:

- In the all-comer study population, given the pre-specified type I error rate of 0.2, the results of Study CFD4870g showed a statistically significant clinical benefit in patients who received monthly lampalizumab treatment over an 18-month study period as assessed by FAF (primary endpoint) and CFP (secondary endpoint). There was no apparent treatment effect observed in the lampalizumab every-other-month all-comer group.
- In a biomarker-positive subgroup, monthly treatment with lampalizumab resulted in a more significant reduction of GA progression; there was also a lampalizumab treatment effect in biomarker-positive patients who were treated every other month. There was no apparent lampalizumab treatment benefit in the biomarker-negative monthly and every-other-month groups. These subgroup analyses suggest that the biomarker may be both prognostic for GA progression and predictive for lampalizumab treatment response. The biomarker results will need to be replicated in larger trials.
- Lampalizumab administered as 10-mg ITV injections monthly or every other month over 18 months demonstrated an acceptable safety and tolerability profile in patients with GA secondary to AMD

Date of the Report

12 March 2014