Sponsor

Novartis

Generic Drug Name

Ranibizumab in combination with verteporfin

Therapeutic Area of Trial

Age-Related Macular Degeneration (AMD)

Approved Indication

Treatment of neovascular (wet) age-related macular degeneration (AMD)

Study Number

CRFB002B2201

Title

Open-Label, Multi-center, Phase II Study Assessing the Safety of ranibizumab Administered in Conjunction with Photodynamic Therapy with verteporfin in Patients with Occult or Predominantly Classic Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration

Phase of Development

Phase II

Study Start/End Dates

25-Nov-2004 to 27-Jul-2007

Study Design/Methodology

An open-label, multi-center study in patients with occult or predominantly classic subfoveal choroidal neovascularization secondary to age-related macular degeneration (AMD.

Investigational treatments were initiated sequentially in 3 cohorts at intervals of at least 30 days based on tolerance of treatment in the preceding cohort. Ranibuizumab was administered as an intravitreal injection to all patients in a multiple-dose regimen of 0.5 mg of ranibizumab at baseline, month 1, month 2, and month 3 for a total of 4 injections.

All patients received photodynamic therapy with verteporfin at baseline administered on the same day and prior to the ranibizumab injection. Patients were to be retreated with verteporfin at month 3, month 6, and month 9 if leakage on the fluorescein angiogram was present during that visit.

Study duration was extended from 9 to 24 months to assess the long-term safety of the combined

treatments of ranibizumab and verteporfin. Patients were offered re-treatment with verteporfin at month 10 (only if not administered at month 9), 12, 15, 18, 21, and 24 and/or re-treatment with 0.3 mg ranibizumab as needed based on predefined criteria.

Pharmacokinetic blood sampling was performed in a subset of 20 patients after the first dose of ranibizumab (ranibizumab with verteporfin) and after the third dose of ranibizumab (not in combination with verteporfin). Venous blood samples were taken 2 hours after intravitreal injection and then on days 1, 3, 7, and 14 post-dose.

Centres

10 centers in 2 countries: Austria (1), Germany (9)

Publication

9-Month results in press

Objectives

Primary objective(s)

- To evaluate the safety of the same-day administration of photodynamic therapy with verteporfin and an intravitreal injection of ranibizumab 0.5 mg.

Secondary objective(s)

- To explore the effect of photodynamic therapy on ranibizumab pharmacokinetics i.e. C_{max}, T_{max}, apparent $T_{1/2}$, and AUC_{0-T} (last measurement time point).
- To explore the effects of treatment on efficacy as assessed by change in visual acuity and change in retinal thickness from baseline.

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

Ranibizumab:

Dose:	0.5 mg intravitreal injection 0.3 mg intravitreal injection

Verteporfin:

Dose:	6 mg of verteporfin/m^2 body surface area
Infusion time:	10 minutes
Light dose:	50 J/cm^2
Light administration:	15 minutes after start of infusion
Light dose rate:	689 mW/cm2
Light delivered for:	83 seconds

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

NA

Criteria for Evaluation

Primary variables

- Primary safety: The incidence of severe vision loss defined as number of patients who lost =30 letters in best corrected visual acuity (BCVA) from baseline, beginning within 14 days of the combination treatment and persisting for longer than 14 days assessed with Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing.

Secondary variables

Safety and tolerability

- The incidence of moderate vision loss at 2m defined as the number of patients who lost = 15 letters in BCVA from baseline, beginning within 14 days of the combination treatment and persisting for longer than 14 days.
- Frequency of Adverse events including incidence of uveitis.

Pharmacokinetics

- Systemic ranibizumab concentration 2 hours after intravitreal injection and on days 1, 3, 7, and 14 post-dose to calculate C_{max}, T_{max}, apparent $T_{1/2}$, and AUC_{0-T}

Other

Statistical Methods

The Intent to treat population for the efficacy analysis consisted of all patients who received combination verteporfin and ranibizumab treatment at baseline and had at least one post-baseline assessment of visual acuity or retinal thickness. The analysis of the exploratory efficacy variables was based on observed data only.

The Safety Population consisted of all patients who received combination verteporfin and ranibizumab treatment at baseline and had at least one post-baseline safety assessment.

Standard pharmacokinetic parameters were derived by noncompartmental methods in WinNonlin (version 5.0.1, Pharsight Corporation, Mountain View, CA, USA) including: the peak concentration Cmax; the time of its occurrence tmax; the area under the concentration-time curve to the last quantifiable serum concentration $AUC_{(0-t)}$ by trapezoidal summation; and the elimination half-life $t_{1/2}$ by log-linear regression. Parameters were summarized by treatment with descriptive

statistics. The test/reference geometric mean ratio for Cmax and for $AUC_{(0-t)}$ was calculated (reference = ranibizumab alone; test = ranibizumab with verteporfin).

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Patients 50 years of age or greater who have provided informed consent.
- Patients with subfoveal choroidal neovascularization lesions secondary to AMD, either predominantly classic or occult with no classic component.
- The total area of CNV (including both classic and occult components) encompassed within the lesion must be = 50% of the total lesion area.
- The greatest linear dimension of the total lesion area must be =5400 microns.
- Patients who have a BCVA score between 73 and 24 letters, inclusively, in the study eye using ETDRS-like grading charts (approximately 20/40 to 20/320).
- Willing to return for all scheduled visits.
- Only one eye is assessed in the study. If both eyes are eligible, the one with the worse visual acuity will be selected for treatment and study unless, based on medical reasons, the investigator deems the other eye the more appropriate candidate for treatment and study.

Exclusion criteria

- Patients who have a BCVA of < 34 letters (approximately 20/200) in both eyes (legally blind is defined as bilateral vision below 20/200 or less than 34 letters).
- Prior treatment in the study eye with verteporfin, external-beam radiation therapy, subfoveal focal laser photocoagulation, vitrectomy, or transpupillary thermotherapy.
- Previous participation in a clinical trial (for either eye) involving anti-angiogenic drugs (pegaptanib, ranibizumab, anecortave acetate, protein kinase C inhibitors, etc.).
- Previous participation in any studies of investigational drugs within one month preceding Day 1(excluding vitamins and minerals).
- Previous or current intravitreal drug delivery (e.g., intravitreal corticosteroid injection or device implantation) in the study eye.
- Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within one month preceding Day 1.
- Concomitant use of chronic NSAIDs or steroids (by any route) for the duration of study participation (chronic use is defined as multiple doses taken daily for three or more consecutive days at any time during the study). Note that ASA (aspirin) taken as “low dose” up to 100 mg qd for prophylaxis of MI and/or stroke is permitted during study.
- Current use or of likely need for systemic medications known to be toxic to the lens, retina or optic nerve, including Deferoxamine, Chloroquine/ hydroxychloroquine (Plaquenil), Tamoxifen, Phenothiazines and Ethambuto is excluded.
- History of glaucoma filtration surgery, corneal transplant surgery or extracapsular extraction of cataract with phacoemulsification within six months preceding Day One, or a history of post-operative complications within the last 12 months preceding Day One in the study eye (uveitis, cyclitis etc.).
- History of uncontrolled glaucoma in the study eye (defined as intraocular pressure = 25

mmHg despite treatment with anti-glaucoma mediation).

- History of submacular surgery or other surgical intervention for AMD in the study eye within two months preceding Day 1.
- Aphakia or absence of the posterior capsule in the study eye.
- Previous violation of the posterior capsule in the study eye is also excluded unless it occurred as a result of YAG posterior capsulotomy in association with prior, posterior chamber intraocular lens implantation
- Spherical equivalent of the refractive error in the study eye demonstrating more than -8 diopters of myopia.
- Presence of a retinal pigment epithelial tear involving the macula in the study eye.
- Angioid streaks or precursors of CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia.
- Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention during the study period to prevent or treat visual loss that might result from that condition, or if allowed to progress untreated, could likely contribute to loss of at least two lines of BCVA over the study period.
- Active intraocular inflammation (grade trace or above) in the study eye.
- Any active infection involving eyeball adnexa.
- Subretinal hemorrhage in the study eye that involves the center of the fovea, if the size of the hemorrhage is either =50% of the total lesion area or =1 disc area in size.
- Subfoveal fibrosis or atrophy in the study eye.
- Vitreous hemorrhage or history of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye.
- Ocular conditions that require chronic concomitant therapy with systemic or topical ocular corticosteroids. Chronic concomitant therapy is defined as multiple doses taken daily for three or more consecutive days at any time within six months prior to screening or during the course of the study.
- Pre-menopausal women not using adequate contraception. The following are considered effective means of contraception: surgical sterilization; use of oral contraceptives; barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel; an IUD; or contraceptive hormone implant or patch.
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications.
- Currently receiving treatment for active systemic infection.
- History of allergy to fluorescein, not amenable to treatment.
- Inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analyzed and graded by the central reading center.
- Inability to comply with study or follow-up procedures.

Number of Subjects

	Novartis product n (%)
Planned	30
Enrolled	32 (100.0)
Intent-to-treat population (ITT)	32 (100.0)
Completed Month 9	30 (93.8)
Discontinued until Month 9	
Total	2 (6.3)
Withdrawn due to adverse events	1 (3.1)
Withdrawn for other reasons	1 (3.1)
Enrolled into 24 months extension	16
Completed Month 24	8
Discontinued before Month 24	8
Withdrawn for other reasons	8

Demographic and Background Characteristics (All patients enrolled)

	Cohort I N=12	Cohort II N=10	Cohort III N=10	All N=32
Age (year)				
N	12	10	10	32
Mean (SD)	77.5 (7.85)	80.1 (6.40)	70.9 (8.23)	76.3 (8.25)
Median	75.5	82.0	73.0	77.0
Range	67 - 93	69 - 87	57 - 83	57 - 93
Sex - n(%)				
Male	3 (25.0)	4 (40.0)	3 (30.0)	10 (31.3)
Female	9 (75.0)	6 (60.0)	7 (70.0)	22 (68.8)
Race - n(%)				
Caucasian	12 (100.0)	10 (100.0)	10 (100.0)	32 (100.0)
Body Surface Area (m^2)				
N	12	10	10	32
Mean (SD)	1.76 (0.178)	1.77 (0.263)	1.89 (0.136)	1.81 (0.201)
Median	1.74	1.72	1.90	1.78
Range	1.54 - 2.15	1.52 - 2.40	1.60 - 2.04	1.52 - 2.40

Ocular baseline characteristics for study eye by cohort (All patients enrolled)

	Cohort I N=12	Cohort II N=10	Cohort III N=10	All N=32
Best Corrected Visual Acuity (4 meters), number of letters				
N	12	10	9	31
Mean (SD)	49.8 (14.02)	47.4 (11.70)	53.1 (18.05)	50.0 (14.32)
Median	47.0	47.5	58.0	49.0
Range	23 - 76	28 - 67	12 - 73	12 - 76
Best Corrected Visual Acuity (2 meters), number of letters				
N	12	10	10	32
Mean (SD)	47.7 (12.51)	50.1 (9.22)	53.7 (15.11)	50.3 (12.36)
Median	49.0	51.5	57.0	51.0

Range	27 - 72	33 - 68	20 - 72	20 - 72
Intraocular Pressure (mmHg)				
N	12	10	10	32
Mean (SD)	14.7 (2.53)	15.0 (3.37)	15.5 (2.32)	15.0 (2.69)
Median	15.0	14.5	15.5	15.0
Range	10 - 18	11 - 21	12 - 19	10 - 21

Baseline fluorescein angiography/fundus photography characteristics for study eye by cohort (All patients enrolled)

	Cohort I N=12	Cohort II N=10	Cohort III N=10	All N=32
CNV Classification				
N	12	10	10	32
Predominantly classic	4 (33.3)	5 (50.0)	4 (40.0)	13 (40.6)
Occult w/o classic	8 (66.7)	5 (50.0)	6 (60.0)	19 (59.4)
Area of Lesion (mm^2)				
N	12	10	10	32
Mean (SD)	10.907 (8.7501)	5.754 (4.5130)	6.688 (4.4920)	7.978 (6.6627)
Median	8.355	4.675	6.355	6.710
Range	0.65 - 26.61	0.93 - 13.76	0.32 - 13.74	0.32 -26.61
Greatest Linear Dimension of CNV Lesion (µm)				
N	12	10	10	32
Mean (SD)	3945.6 (2075.39)	3027.7 (1397.52)	3010.8 (1227.03)	3366.6 (1655.34)
Median	3570.0	2685.0	3265.0	3325.0
Range	960 - 7657*	1300 - 5390	710 - 4470	710 - 7657
Area of Leakage seen on FA at 10 min (mm^2)				
N	11	10	10	31
Mean (SD)	10.351 (7.8490)	7.000 (5.9605)	6.968 (4.5381)	8.179 (6.3288)
Median	8.880	3.815	5.420	5.690
Range	1.33 - 24.35	1.15 - 19.80	1.05 - 14.40	1.05 - 24.35

FA – fluorescein angiography

Primary Objective Result(s)

Number (%) of patients with severe vision loss in the study eye as defined per protocol after combination treatment by cohort (Safety population)

	Cohort I N=12	Cohort II N=10	Cohort III N=10	All N=32
	n (%)	**n (%)**	**n (%)**	**n (%)**
With severe vision loss*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*severe vision loss is defined as a decrease in BCVA of 30 letters or more that begins within 14 days of the combination treatment and persists for longer than 14 days.

Secondary Objective Result(s)

Pharmacokinetics:

Ranibizumab pharmacokinetic parameters

Parameter	Ranibizumab alone	Ranibizumab + verteporfin
N	17	20
t_{max} (days)	1 (0.08 – 7)	1 (0.08 – 3)
C_{max} (ng/ml)	1.8 ± 1.1	1.6 ± 0.9
$AUC_{(0-t)}$ (ng.day/ml)	8.9 ± 3.9	8.1 ± 4.0
$t_{1/2}$ (days)	6.7 ± 3.7	5.6 ± 2.6

Data are arithmetic mean ± sd except for tmax which is median (range).

Safety Results

Non-ocular Adverse Events by System Organ Class – (Safety population -9- Month data)

	Cohort I N=12	Cohort II N=10	Cohort III N=10	All N=32
	n (%)	n (%)	n (%)	n (%)
Patients with non-ocular AEs	4 (33.8)	7 (70.0)	8 (80.0)	19 (59.4)
Patients with drug-related non-ocular AE	0	1 (10.0)	1 (10.0)	2 (6.3)
Drug-related non-ocular AEs by primary system organ class				
General disorders & administration site conditions	0	1 (10.0)	0	1 (3.1)
Muscoskeletal and connective tissue disorders	0	0	1 (10.0)	1 (3.1)

During the period from Month 9 to 24 there was no additional non-ocular events suspected to be related to study drug reported.

Ocular Adverse Events by System Organ Class – (9 Month data)

	Cohort I N=12	Cohort II N=10	Cohort III N=10	All N=32
	n (%)	n (%)	n (%)	n (%)
Patients with ocular AEs	8 (66.7)	6 (60.0)	10 (100)	24 (75.0)
Patients with drug-related ocular AE	6 (50.0)	4 (40.0)	2 (20.0)	12 (37.5)
Drug-related AEs by primary system organ class				
Eye disorders	6 (50.0)	3 (30.0)	1 (10.0)	10 (31.3)
General disorders & administration site conditions	1 (8.3)	0	0	1 (3.1)
Investigations	0	1 (10.0)	1 (10.0)	2 (6.3)

During the period from Month 9 to 24 there was no additional ocular events suspected to be related to study drug reported.

Most Frequently Reported non-ocular AEs Overall by Preferred Term and Cohort n - (%) (Safety population – 9- Month data)

	Cohort I N=12	Cohort II N=10	Cohort III N=10	All N=32
	n (%)	n (%)	n (%)	n (%)
Total no. of patients with non-ocular Adverse events	4 (33.3)	7 (70.0)	8 (80.0)	19 (59.4)
Non-ocular Adverse events				
Back pain	0 (0.0)	1 (10.0)	2 (20.0)	3 (9.4)
Hypertension	0 (0.0)	2 (20.0)	1 (10.0)	3 (9.4)
Abdominal pain	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.1)
Abdominal pain upper	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.1)
Angina pectoris	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.1)
Atrial fibrillation	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.1)
Bronchial irritation	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.1)
Bronchitis	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.1)
Cough	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.1)
Diarrhoea	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.1)

Five patients out of 16 continuing after Month 9 reported additional non-ocular AEs in the period from Month 9 to Month 24.

Most Frequently Reported ocular AEs Overall by Preferred Term and Cohort - n (%) (Safety population – 9 Month data)

	Cohort I N=12	Cohort II N=10	Cohort III N=10	All N=32
	n (%)	n (%)	n (%)	n (%)
Total no. of patients with ocular Adverse events	8 (66.7)	6 (60.0)	10 (100)	24 (75.0)
Ocular Adverse events				
Visual acuity reduced	3 (25.0)	1 (10.0)	2 (20.0)	6 (18.8)
Ocular hyperemia	3 (25.0)	1 (10.0)	1 (10.0)	5 (15.6)
Eye pain	2 (16.7)	1 (10.0)	1 (10.0)	4 (12.5)
Intraocular pressure increased	2 (16.7)	1 (10.0)	1 (10.0)	4 (12.5)
Eye pruritus	0 (0.0)	1 (10.0)	2 (20.0)	3 (9.4)
Blepharitis	1 (8.3)	0 (0.0)	1 (10.0)	2 (6.3)
Conjunctivitis	1 (8.3)	1 (10.0)	0 (0.0)	2 (6.3)
Retinal hemorrhage	0 (0.0)	0 (0.0)	2 (20.0)	2 (6.3)
Vision blurred	2 (16.7)	0 (0.0)	0 (0.0)	2 (6.3)
Vitreous disorder	0 (0.0)	1 (10.0)	1 (10.0)	2 (6.3)

During the period from Month 9 to 24 three patients experienced additional ocular adverse events in the study eye.

Serious Adverse Events and Deaths

Number (%) of patients who died, had serious ocular or non-ocular AEs, discontinued because of ocular or non-ocular AEs (Safety population – 9-Month data)

	Cohort I N=12	Cohort II N=10	Cohort III N=10	All N=32
Patients studied				
Total no. of patients	12	10	10	32
Patients with ocular AE(s)	8 (66.7)	6 (60.0)	10 (100)	24 (75.0)
Patients with non-ocular AE(s)	4 (33.3)	7 (70.0)	8 (80.0)	19 (59.4)
Serious or significant AEs				
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ocular SAEs in study eyes	1 (8.3)	0 (0.0)	1 (10.0)	2 (6.3)
Ocular SAEs in fellow eyes	0 (0.0)	0 (0.0)	1 (0.0)	1 (3.1)
Non-ocular SAEs	2 (16.7)	1 (10.0)	3 (30.0)	6 (18.8)
Discontinued due to ocular AEs in study eyes	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.1)
Discontinued due to ocular AEs in fellow eyes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to non-ocular AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

9-Month:

Ocular SAE in study eye: retinal pigment epithelial tear (1), decrease in visual acuity (1)
Ocular SAE in fellow eye: decrease in visual acuity (1)
Non-Ocular SAE: systemic lupus erythematosus (1), peripheral edema of both legs (1), angina

pectoris (1), abdominal pain (1), hot flush (1), fracture of the humerus (1)

Month 9 to 24:

No additional serious ocular adverse events were reported in patients continuing after Month 9. One of the 16 patients continuing reported an additional non-ocular SAE after Month 9 (endometrial hyperplasia)

Number (%) of patients with moderate vision loss in the study eye as defined per protocol after combination treatment by cohort (Safety population)

	Cohort I N=12	Cohort II N=10	Cohort III N=10	All N=32
	n (%)	n (%)	n (%)	n (%)
With moderate vision loss[+]	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.1)

[+]moderate vision loss is defined as a decrease in BCVA of 15 letters or more that begins within 14 days of the combination treatment and persists for longer than 14 days.

Date of Clinical Trial Report

9-Month CSR (11-Dec-2007)

9-Month CSR Addendum 1 (28-Nov-2008)

24-Month CSR (31-Mar-2008)

Date Inclusion on Novartis Clinical Trial Results Database

August 8, 2008

Date of Latest Update

November 28, 2008