Sponsor

Alcon Research, Ltd.

Generic Drug Name

AL-39324 Suspension

Trial Indication(s)

Exudative age-related macular degeneration (AMD)

Protocol Number

C-09-023

Protocol Title

A Dose-Escalation Study of AL-39324 Suspension versus Lucentis® for the Treatment of Exudative Age-Related Macular Degeneration

Clinical Trial Phase

Phase II

Study Start/End Dates

16 June 2010 / 11 May 2011

Reason for Termination

Not applicable

Study Design/Methodology

This was a prospective, controlled, randomized, treatment-masked, multicenter, dose-escalation study.

Centers

Subjects were recruited from 15 investigational sites located in the United States (5), Australia (3), Israel (2), Switzerland (2), Germany (1), Austria (1), and Italy (1).

Objectives

The primary objective was to assess the safety, tolerability and the effects of treatment on ocular outcomes following a single intravitreal administration of AL-39324 suspension in patients with exudative AMD. Following a single administration, patients were followed for 6 months postinjection.

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

Test Product: AL-39324 1.00 mg/mL
Dose: 100 µL
Mode of Administration: Intravitreal injection

Test Product: AL-39324 2.00 mg/mL
Dose: 100 µL
Mode of Administration: Intravitreal injection

Test Product: AL-39324 3.00 mg/mL
Dose: 100 µL
Mode of Administration: Intravitreal injection

Test Product: AL-39324 4.00 mg/mL
Dose: 100 µL
Mode of Administration: Intravitreal injection

Test Product: AL-39324 4.50 mg/mL
Dose: 100 µL
Mode of Administration: Intravitreal injection

Reference Product: Lucentis 10 mg/mL
Dose: 50 µL
Mode of Administration: intravitreal injection

Statistical Methods

The primary efficacy variable was change from baseline in central foveal thickness (CFT) at Month 1. CFT was assessed using optical coherence tomography imaging and summarized by treatment group using descriptive statistics.

Analysis of the primary safety variable, the incidence of targeted adverse events that occurred in the study eye within 7 days of the intravitreal injection, was summarized by treatment group.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Willing to give written informed consent, make the required study visits and follow instructions;
- The study eye:
    - must have a primary diagnosis of choroidal neovascularization (CNV) secondary to AMD
    - lesion must be no larger than 30 mm2
    - must have edema measuring greater than 340 µm
    - must have a visual score between 73 and 34 letters, inclusive
    - must be able to have clear picture taken of the back of the eye

Exclusion Criteria:

- The study eye must not have been treated for exudative AMD previously
- The study eye must not have any other ocular disease, condition, infection, or recent surgery that would interfere with vision or examination of the back of the eye
- The study eye must not have uncontrolled glaucoma
- The study eye must not be missing a lens
- Must not be taking any medication that is toxic to the lens
- Must not be taking oral or ocular corticosteroids
- Must not have an unstable or progressive condition that would interfere with study visits

- Must not have allergies to any component of the test article or sensitivity to fluorescein dye
- If female, must not be pregnant or nursing and must agree to adequate birth control
- Must not be participating in another drug or device study within 30 days of screening for this study

Participant Flow Table

	AL-39324 100 µg	AL-39324 200 µg	AL-39324 300 µg	AL-39324 400 µg	AL-39324 450 µg	Lucentis
Started (Randomized to treatment)	5	5	5	5	5	10
Safety Analysis Set	5	5	5	5	5	10
Intent-to Treat (ITT) Analysis Set	5	5	5	5	5	10
Completed Study	5	5	5	5	5	10
Discontinued	0	0	0	0	0	0

Baseline Characteristics

Gender Demographic Statistics
(Intent to Treat)

Gender	AL-39324 100 µg	AL-39324 200 µg	AL-39324 300 µg	AL-39324 400 µg	AL-39324 450 µg	Lucentis
Male	1	2	1	1	1	4
Female	4	3	4	4	4	6

Categorical Age Demographic Statistics
(Intent to Treat)

Age (years)	AL-39324 100 µg	AL-39324 200 µg	AL-39324 300 µg	AL-39324 400 µg	AL-39324 450 µg	Lucentis
50-64	1	0	0	0	1	0
≥65	4	5	5	5	4	10

Summary of Efficacy

There was no clear pattern to the mean reduction from baseline to Month 1 in CFT among AL-39324 doses.

Primary Outcome Results

Descriptive Statistics for Central Foveal Thickness (microns), Change from Baseline at Month 1 (Intent to Treat)

	AL-39324 100 µg	AL-39324 200 µg	AL-39324 300 µg	AL-39324 400 µg	AL-39324 450 µg	Lucentis
N	5	5	5	5	5	10
Mean	-85	-110	-32.4	-93.6	-141.2	-125.3
Median	-89	-64	-64	-57.0	-140.0	-132.5
SD	89	115.6	101.2	134.5	133.1	79.1
(Min, Max)	(-224, 3)	(-286, -8)	(-123, 99)	(-319, 36)	(-325, 46)	(-265, -17)
95% CI	(-195.6, 25.6)	(-253.5, 33.5)	(-158.1, 93.3)	(-260.6, 73.4)	(-306.4, 24.0)	(-181.9, -68.7)

SD = Standard Deviation, CI = Confidence Interval

Secondary Outcome Results

None reported.

Summary of Safety

The use of AL-39324 was considered unsafe due to increases in intraocular pressure observed in all AL-39324 treatment groups that were uncharacteristic in nature. The mechanism of action for the increases in intraocular pressure is currently unknown.

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Primary Safety Results

Incidence of Patients With Targeted Adverse Events Occurring In the Study Eye Within 7 Days of Intravitreal Injection (Safety Population)

	AL-39324 100 µg		AL-39324 200 µg		AL-39324 300 µg		AL-39324 400 µg		AL-39324 450 µg		Lucentis	
	Total	N (%)	Total	N (%)	Total	N (%)	Total	N (%)	Total	N (%)	Total	N (%)
Overall	5	0 (0.0)	5	0 (0.0)	5	0 (0.0)	5	0 (0.0)	5	1 (20.0)	10	0 (0.0)
Adults	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	0 (0.0)	0	0 (0.0)
Elderly	4	0 (0.0)	5	0 (0.0)	5	0 (0.0)	5	0 (0.0)	4	1 (25.0)	10	0 (0.0)

Adults - 50 to 64 years; Elderly - 65 years or older

Targeted adverse events were defined as:

- 4+ ocular inflammation;
- 2-3+ ocular inflammation that failed to decrease to 1+ or less within 30 days of the onset of the event;
- 30 letter decrease in BCVA compared with pre-injection visual acuity;
- sustained (>15 minutes) loss of light perception due to elevated IOP;
- 20 mmHg increase or decrease in IOP not returning to pre-injection levels within 7 days of the onset of the event;
- new retinal tear or detachment;
- new vitreous hemorrhage of > 2+ severity unresolved within 14 days of the onset of the event;
- new retinal hemorrhage > 1 disc area in size and involving the fovea; or
- increase of previous retinal hemorrhage by > 1 disc area in size and involving the fovea

Serious Adverse Events

Four participants had a serious adverse event: 2 in the AL-39324 100 µg group, 1 in the AL-39324 400 µg group, and 1 in the AL-39324 450 µg group.

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All Adverse Events by System Organ Class

	AL-39324 100 µg		AL-39324 200 µg		AL-39324 300 µg		AL-39324 400 µg		AL-39324 450 µg		Lucentis	
	N	%	N	%	N	%	N	%	N	%	N	%
RELATED TO TEST ARTICLE												
Eye disorders												
Visual acuity reduced			1	20	1	20	1	20	2	40		
Vitreous opacities	1	20							2	40		
Anterior chamber cell			1	20								
Eye irritation	1	20										
Myodesopsia					1	20						
Investigations												
Intraocular pressure increased					1	20	1	20	1	20		
RELATED TO PROCEDURE												
Eye disorders												
Myodesopsia							1	20				
Visual impairment									1	20		
Investigations												
Intraocular pressure increased	1	20										
NOT RELATED												
Blood and lymphatic system disorders												
Red blood cell abnormality							1	20				
Cardiac disorders												
Atrial tachycardia	1	20										
Cardiac failure congestive	1	20										
Ear and labyrinth disorders												
Vertigo							1	20				

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	AL-39324 100 µg		AL-39324 200 µg		AL-39324 300 µg		AL-39324 400 µg		AL-39324 450 µg		Lucentis	
	N	%	N	%	N	%	N	%	N	%	N	%
Eye disorders												
Macular oedema	2	40	1	20			2	40				
Conjunctival hyperaemia	1	20			1	20			1	20		
Retinal haemorrhage					1	20	2	40				
Myodesopsia	1	20			1	20						
Corneal opacity					1	20						
Macular degeneration											1	10
Maculopathy							1	20				
Photopsia	1	20										
Punctate keratitis					1	20						
Retinal cyst							1	20				
Vitreous detachment											1	10
Gastrointestinal disorders												
Gastritis							1	20				
Nausea					1	20						
Hepatobiliary disorders												
Bile duct stone							1	20				
Infections and infestations												
Tooth infection											1	10
Upper respiratory tract infection									1	20		
Urinary tract infection					1	20						
Injury, poisoning and procedural complications												
Injury	1	20										
Investigations												
Intraocular pressure increased							1	20	1	20		

	AL-39324 100 µg		AL-39324 200 µg		AL-39324 300 µg		AL-39324 400 µg		AL-39324 450 µg		Lucentis	
	N	%	N	%	N	%	N	%	N	%	N	%
Blood glucose increased											1	10
Blood urea nitrogen/creatinine ratio increased					1	20						
Haematocrit abnormal							1	20				
Haemoglobin abnormal							1	20				
Platelet count abnormal							1	20				
White blood cells urine positive	1	20										
Nervous system disorders												
Headache							1	20				
Migraine							1	20				
Renal and urinary disorders												
Nephrolithiasis	1	20										
Skin and subcutaneous tissue disorders												
Urticaria	1	20										
Surgical and medical procedures												
Skin neoplasm excision	1	20										
Tooth extraction							1	20				
Vascular disorders												
Hypertension					1	20						

Other Relevant Findings

There are no other relevant findings to disclose.

Date of Clinical Trial Report

16-Dec-2011