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Novartis Clinical Trial Results

Sponsor

Alcon Research

Generic Drug Name

Brolucizumab

Trial Indication(s)

Age-Related Macular Degeneration

Protocol Number

C-10-083

Protocol Title

Safety and Efficacy Study of ESBA1008 Versus LUCENTIS® for the Treatment of Exudative Age-Related Macular Degeneration

Clinical Trial Phase

Phase I/II

Phase of Drug Development

Phase I/II

Study Start/End Dates

October 2010 to March 2013

Reason for Termination

Not applicable.

Study Design/Methodology

This was a prospective, multicenter, double-masked, randomized, single-dose ascending, active-controlled, parallel-group study intended to evaluate the safety and efficacy of a single intravitreal administration of ESBA1008 solution compared with LUCENTIS in patients with primary subfoveal choroidal neovascularization (CNV) secondary to AMD.

Patients were initially randomized (5:2) within dosing cohorts to receive either ESBA1008 (0.5, 3.0, and 4.5 mg) or LUCENTIS. The objective of this period of the study was to identify the maximum tolerated dose (MTD) among the 3 tested doses of ESBA1008. Specifically, the MTD was the dose level below which the dose escalation stopping criteria were met or was the highest tested dose if the stopping criteria were not met. Once the MTD was determined, a subsequent expansion of the cohort occurred with patients randomized in a 1:1 ratio to receive ESBA1008 at the MTD or LUCENTIS (the MTD expansion period of the study). Evaluation of an additional cohort of a 6.0-mg ESBA1008 dose occurred in parallel with the MTD expansion portion; the addition of the 6.0-mg dose and the increase in numbers of patients in the 3.0 mg and 0.5 mg dose levels were added as protocol amendments. If the 6.0-mg dose was assessed to be safe and well tolerated, then it was tested as an additional expansion arm with LUCENTIS in parallel with the MTD expansion portion.

Enrolled patients were evaluated for safety and efficacy across 13 study visits. These visits included Screening (Visit 1), Randomization (Day 0; Visit 2), and 11 posttreatment visits (Day 1 [Visit 3], Week 1 [Visit 4], Week 2 [Visit 5], and Months 1, 1.5, 2, 2.5, 3, 4, 5, and 6 [Visit 6 through Visit 13/Exit]).

Centers

This study included 51 investigational centers in the United States, Europe, Israel, and Australia.

Objectives:

Primary objective(s)

Primary Objective: to evaluate change from baseline at month 1 in central subfield thickness (CSFT) as measured by spectral domain ocular coherence tomography (SD-OCT)

Secondary objective(s)

To evaluate duration of effect measured by the time from randomization to receipt of standard of care as determined by the investigator based on protocol criteria

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

ESBA1008 solution administered as a single intravitreal injection (Dose A, Dose B, Dose C, Dose D).

Statistical Methods

The intent-to-treat (ITT) analysis set included all patients who were randomized, received study drug and completed at least 1 scheduled on-therapy study visit. The per protocol (PP) analysis set included all patients who were randomized, received study drug, satisfied pre randomization inclusion/exclusion criteria, and completed at least 1 scheduled on-therapy study visit. In addition, individual patient visits and data points that did not satisfy the protocol criteria deemed important in the interpretation of efficacy may have been excluded from the PP analysis set. The safety analysis set included all patients who received study drug.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Provide written informed consent.
- Primary subfoveal choroidal neovascularization (CNV) secondary to AMD, including predominantly classic, minimally classic or occult lesions, in the study eye.
- New diagnosis of wet AMD or evidence of recent disease progression within the last 3 months in study eye.
- Evidence of subretinal fluid or retinal cystic changes with a CSFT of > 340 µm using a Spectralis SD-OCT (Heidelberg Engineering) imaging system.
- Best-corrected visual acuity (BCVA) of Snellen equivalent 20/200 or better in the non-study eye.
- Other protocol-defined inclusion criteria may apply.

Exclusion criteria

- Previously administered therapy, approved or investigational, for wet AMD in the study eye.
- Any current or history of macular or retinal disease in the study eye other than wet AMD.
- Lasik or cataract surgery within the last 3 months in the study eye or expected to have cataract removal surgery during the study.
- Uncontrolled or advanced glaucoma in the study eye.
- Use of systemic or topical ocular corticosteroids.
- History of a medical condition that, in the opinion of the Investigator, would preclude scheduled visits, completion of the study, or safe administration of study medication.
- Abnormal or unsuitable laboratory results at Screening visit.
- Lactating or pregnant. Women of childbearing potential must use adequate birth control for the duration of the study.
- Other protocol-defined exclusion criteria may apply.

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Participant Flow Table

	ESBA1008 Dose A	ESBA1008 Dose B	ESBA1008 Dose C	ESBA1008 Dose D	Lucentis
Started	10	35	48	40	61
Completed	10	35	47	39	60
Not Completed	0	0	1	1	1
Adverse Event	0	0	0	0	1
Decision Unrelated to an Adverse Event	0	0	1	1	0

Baseline Characteristics

This analysis population includes all patients who were randomized, received study drug, and completed at least 1 scheduled on-therapy study visit (ITT).

		ESBA1008 Dose A	ESBA1008 Dose B	ESBA1008 Dose C	ESBA1008 Dose D	Lucentis	Total
	N	10	35	48	40	61	194
Age (years)	Mean	75.9	78.5	75.2	74.5	77.8	76.5
	SD	6.9	8.3	7.7	9.8	8.1	8.4
Sex – n (%)	Female	6	15	27	25	33	106
	Male	4	20	21	15	28	88

Primary Outcome Result(s)

Change From Baseline at Month 1 in Central Subfield Thickness (CSFT) as Measured by Spectral Domain Ocular Coherence Tomography (SD-OCT) ITT Population

	ESBA1008 Dose A	ESBA1008 Dose B	ESBA1008 Dose C	ESBA1008 Dose D	Lucentis
Overall Number of Participants Analyzed	10	35	48	40	61
Change From Baseline at Month 1 in Central Subfield Thickness (CSFT) as Measured by Spectral Domain Ocular Coherence Tomography (SD-OCT) [Mean (Standard Deviation)] Unit of measure: microns	-142.3 (78.8)	-181.6 (107.2)	-175.6 (138.9)	-174.9 (101.3)	-159.4 (110.1)

Secondary Outcome Result(s)

Duration of Effect Measured by the Time From Randomization to Receipt of Standard of Care as Determined by the Investigator Based on Protocol Criteria (ITT Population)

	ESBA1008 Dose A	ESBA1008 Dose B	ESBA1008 Dose C	ESBA1008 Dose D	Lucentis
Overall Number of Participants Analyzed	10	35	48	40	61
Duration of Effect Measured by the Time From Randomization to Receipt of Standard of Care as Determined by the Investigator Based on Protocol Criteria Median [(Inter-Quartile Range) Unit of measure: Days]	45 (30 to 60)	75 (45 to 120)	67.5 (37.5 to 120)	75 (37.5 to 150)	45 (25 to 75)

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Safety Results

Serious Adverse Events

	ESBA1008	ESBA1008	ESBA1008	ESBA1008	Lucentis
	Affected/At Risk	Affected/At Risk	Affected/At Risk	Affected/At Risk	Affected/At Risk
Total	0/11 (0%)	4/31 (12.9%)	3/47 (6.38%)	3/44 (6.82%)	7/61 (11.48%)
Cardiac disorders					
Acute myocardial infarction [A] †	0/11 (0%)	0/31 (0%)	0/47 (0%)	1/44 (2.27%)	0/61 (0%)
Eye disorders					
Visual acuity reduced [A] †	0/11 (0%)	1/31 (3.23%)	0/47 (0%)	1/44 (2.27%)	0/61 (0%)
Gastrointestinal disorders					
Pancreatitis acute [A] †	0/11 (0%)	0/31 (0%)	0/47 (0%)	1/44 (2.27%)	0/61 (0%)

	ESBA1008	ESBA1008	ESBA1008	ESBA1008	Lucentis
	Affected/At Risk	Affected/At Risk	Affected/At Risk	Affected/At Risk	Affected/At Risk
General disorders					
Multi-organ failure [A] †	0/11 (0%)	0/31 (0%)	0/47 (0%)	1/44 (2.27%)	0/61 (0%)
Hepatobiliary disorders					
Hepatitis [A] †	0/11 (0%)	0/31 (0%)	1/47 (2.13%)	0/44 (0%)	0/61 (0%)
Infections and infestations					
Cellulitis [A] †	0/11 (0%)	0/31 (0%)	0/47 (0%)	0/44 (0%)	1/61 (1.64%)
Endophthalmitis [A] †	0/11 (0%)	0/31 (0%)	0/47 (0%)	0/44 (0%)	1/61 (1.64%)
Pneumonia [A] †	0/11 (0%)	0/31 (0%)	0/47 (0%)	0/44 (0%)	2/61 (3.28%)
Injury, poisoning and procedural complications					
Post-procedural haematoma [A] †	0/11 (0%)	0/31 (0%)	0/47 (0%)	1/44 (2.27%)	0/61 (0%)
Nervous system disorders					
Cerebrovascular accident [A] †	0/11 (0%)	1/31 (3.23%)	0/47 (0%)	0/44 (0%)	1/61 (1.64%)
Syncope [A] †	0/11 (0%)	1/31 (3.23%)	0/47 (0%)	0/44 (0%)	0/61 (0%)
Transient ischaemic attack [A] †	0/11 (0%)	1/31 (3.23%)	0/47 (0%)	0/44 (0%)	0/61 (0%)
Vertebrobasilar insufficiency [A] †	0/11 (0%)	0/31 (0%)	1/47 (2.13%)	0/44 (0%)	0/61 (0%)
Respiratory, thoracic and mediastinal disorders					
Acute respiratory failure [A] †	0/11 (0%)	0/31 (0%)	0/47 (0%)	1/44 (2.27%)	0/61 (0%)
Chronic obstructive pulmonary	0/11 (0%)	0/31 (0%)	1/47 (2.13%)	0/44 (0%)	0/61 (0%)
Dyspnoea [A] †	0/11 (0%)	0/31 (0%)	0/47 (0%)	0/44 (0%)	1/61 (1.64%)

Pulmonary oedema A †	0/11 (0%)	1/31 (3.23%)	0/47 (0%)	0/44 (0%)	0/61 (0%)
Skin and subcutaneous tissue disorders					
Blister A †	0/11 (0%)	0/31 (0%)	1/47 (2.13%)	0/44 (0%)	0/61 (0%)
Surgical and medical procedures					
Aortic bypass A †	0/11 (0%)	0/31 (0%)	0/47 (0%)	0/44 (0%)	1/61 (1.64%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.0

Adverse Events by System Organ Class (5%)

	ESBA1008	ESBA1008	ESBA1008	ESBA1008	Lucentis
	Affected/At Risk	Affected/At Risk	Affected/At Risk	Affected/At Risk	Affected/At Risk
Total	1/11 (9.09%)	10/31 (32.26%)	17/47 (36.17%)	16/44 (36.36%)	13/61 (21.31%)
Eye disorders					
Conjunctival haemorrhage A †	0/11 (0%)	3/31 (9.68%)	3/47 (6.38%)	8/44 (18.18%)	2/61 (3.28%)
Eye pain A †	0/11 (0%)	0/31 (0%)	4/47 (8.51%)	1/44 (2.27%)	1/61 (1.64%)
Retinal haemorrhage A †	0/11 (0%)	1/31 (3.23%)	2/47 (4.26%)	1/44 (2.27%)	4/61 (6.56%)
Visual acuity reduced A †	0/11 (0%)	2/31 (6.45%)	1/47 (2.13%)	2/44 (4.55%)	3/61 (4.92%)
Infections and infestations					
Bronchitis A †	0/11 (0%)	0/31 (0%)	3/47 (6.38%)	0/44 (0%)	3/61 (4.92%)
Nasopharnygitis A †	1/11 (9.09%)	0/31 (0%)	3/47 (6.38%)	3/44 (6.82%)	2/61 (3.28%)
Pneumonia A †	0/11 (0%)	1/31 (3.23%)	0/47 (0%)	0/44 (0%)	3/61 (4.92%)

Urinary tract infection [A] †	0/11 (0%)	4/31 (12.9%)	1/47 (2.13%)	2/44 (4.55%)	0/61 (0%)
Musculoskeletal and connective tissue disorders					
Back pain [A] †	0/11 (0%)	0/31 (0%)	3/47 (6.38%)	0/44 (0%)	1/61 (1.64%)
Vascular disorders					
Hypertension [A] †	0/11 (0%)	1/31 (3.23%)	5/47 (10.64%)	2/44 (4.55%)	0/61 (0%)

Conclusion:

The present study represents the first evaluation of ESBA1008 in humans and was designed to investigate the safety, tolerability, and effects of treatment on ocular outcomes following a single intravitreal injection of ESBA1008 in 4 ascending clinical dose levels (0.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg). Overall, ESBA1008 at doses of both 4.5 and 6.0 mg was effective in patients with primary subfoveal CNV secondary to AMD and was noninferior to LUCENTIS in regard to the mean change from Baseline to Month 1 in CSFT. A trend toward a longer duration of effect was also observed in each ESBA1008 group relative to LUCENTIS. No safety issues were identified that would preclude further clinical development of ESBA1008 up to 6.0 mg.

Date of Clinical Trial Report

24-Apr-2014