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## Sponsor

Alcon Research, Ltd.

## Generic Drug Name

Anecortave Acetate (AA) 15 mg or 30 mg

## Trial Indication(s)

Prevention of the progression of non-exudative to exudative age-related macular degeneration (AMD)

## Protocol Number

C-02-60

## Protocol Title

An Evaluation of Efficacy and Safety of Posterior Juxtascleral Administrations of Anecortave Acetate for Depot Suspension (15 mg or 30 mg) versus Sham Administration in Patients (Enrolled in Study “A” or Study “B”) at Risk for Developing Sight-Threatening Choroidal Neovascularization (CNV) Due to Exudative Age-Related Macular Degeneration (AMD)

## Clinical Trial Phase

Phase 3

## Study Start/End Dates

01Mar 2004 to 13 Jan 2009

## Reason for Termination

Product development was terminated for this use. All active patients were scheduled for a final visit (to include an assessment of safety, visual acuity, and CNV status), 6 months following the patient’s last injection. All active patients had completed study visits through at least Month 24 prior to study termination.

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## Study Design/Methodology

This was a multi-center, double-masked, parallel group, randomized, sham injection- and vehicle-controlled trial.

## Centers

Subjects were recruited from 116 investigational sites located in the US (75), Brazil (5), France (4), Germany (4), UK (4), Australia (3), Canada (3), Italy (3), Sweden (3), Netherlands (2), Spain (2), Austria (1), Belgium (1), Denmark (1), Hungary (1), Northern Ireland (1), Poland (1), Portugal (1) and Switzerland (1).

## Objectives

The primary objective was to demonstrate that Anecortave Acetate for Depot Suspension (15 mg or 30 mg) is safe and effective in arresting the progression of non-exudative (dry) AMD in patients who are at-risk for progressing to exudative (wet) AMD.

## Test Product, Dose, and Mode of Administration

**Test Product**: Anecortave Acetate, 15 mg or 30 mg
Dose: One 0.5 mL injection of 30 mg/mL Anecortave Acetate Sterile Suspension (AA 15 mg) or one 0.5 mL injection of 60 mg/mL Anecortave Acetate Sterile Suspension (AA 30 mg)
Mode of Administration: One injection into a posterior juxtascleral depot (PJD) at 6-month intervals

**Reference Product:** Anecortave Acetate Vehicle (sham AA vehicle)
Dose: One 0.5 mL sham injection of Anecortave Acetate Vehicle
Mode of Administration: One sham injection at 6-month intervals (syringe containing AA vehicle was not inserted into the eye)

## Statistical Methods

The primary statistical objective was to describe the incidence of ST-CNV in patients treated with AA 15 mg or AA 30 mg by PJD and in patients receiving sham injections of AA vehicle.

- Safety: included all randomized patients who received study drug
- ITT: included patients who received study drug and had at least 1 on-therapy visit

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## Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Presents with exudative (wet) AMD in 1 eye (non-study eye) and non-exudative (dry) AMD in the other eye (study eye)
- Meets protocol-specified criteria for qualification and contraception
- Voluntarily consents to participate and provides written informed consent prior to any protocol-specific procedures

Exclusion criteria:

- Uses medications outside protocol-specified parameters
- Has signs, symptoms or history of any condition that, per protocol or in the opinion of the investigator, might compromise:
  1. the safety or well-being of the participant or study staff
  2. the safety or well-being of the participant's offspring (such as through or breast-feeding)
  3. the analysis of results

## Participant Flow Table

**With Reasons for Patient Discontinuation Prior to Month 24**
**(Intent-to-Treat Data)**

| | Total | | AA 15 mg | | AA 30 mg | | Sham | |
|---|---|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Started** | 2546 | 100.0 | 845 | 100.0 | 849 | 100.0 | 852 | 100.0 |
| **Completed** | 1937 | 76.1 | 628 | 74.3 | 642 | 75.6 | 667 | 78.3 |
| **Discontinued** | 609 | 23.9 | 217 | 25.7 | 207 | 24.4 | 185 | 21.7 |
| *Reasons for discontinuation* | | | | | | | | |
| Adverse Event | 136 | 5.3 | 48 | 5.7 | 46 | 5.4 | 42 | 4.9 |
| Lost to Follow-Up | 19 | 0.7 | 6 | 0.7 | 7 | 0.8 | 6 | 0.7 |
| Decision Unrelated to an Adverse Event | 152 | 6.0 | 51 | 6.0 | 55 | 6.5 | 46 | 5.4 |
| Noncompliance | 13 | 0.5 | 4 | 0.5 | 5 | 0.6 | 4 | 0.5 |
| Development of ST-CNV | 234 | 9.2 | 89 | 10.5 | 75 | 8.8 | 70 | 8.2 |
| Other: Not specified | 55 | 2.2 | 19 | 2.2 | 19 | 2.2 | 17 | 2.0 |

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## Baseline Characteristics

**Baseline Patient Characteristics**

**(Intent-to-Treat Data)**

| | Total | | AA 15 mg | | AA 30 mg | | Sham | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| **Total** | 2546 | 100.0 | 845 | 100.0 | 849 | 100.0 | 852 | 100.0 |
| **Age** | | | | | | | | |
| Adults (50 - < 65 years) | 222 | 8.7 | 78 | 9.2 | 74 | 8.7 | 70 | 8.2 |
| Elderly (≥ 65 years) | 2324 | 91.3 | 767 | 90.8 | 775 | 91.3 | 782 | 91.8 |
| **Sex** | | | | | | | | |
| Male | 1091 | 42.9 | 392 | 46.4 | 352 | 41.5 | 347 | 40.7 |
| Female | 1455 | 57.1 | 453 | 53.6 | 497 | 58.5 | 505 | 59.3 |
| **Geography** | | | | | | | | |
| US/Canada | 1769 | 69.5 | 590 | 69.8 | 585 | 68.9 | 594 | 69.7 |
| International | 777 | 30.5 | 255 | 30.2 | 264 | 31.1 | 258 | 30.3 |

## Summary of Efficacy

## Primary Outcome Measure

**Proportion of Patients with CNV (Intent-to-Treat Data)**

| | AA 15 mg | | | | AA 30 mg | | | | Sham AA vehicle | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CNV | | No CNV | | CNV | | No CNV | | CNV | | No CNV | |
| | N | % | N | % | N | % | N | % | N | % | N | % |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Month 6 | 35 | 4.2 | 795 | 95.8 | 28 | 3.4 | 798 | 96.6 | 37 | 4.4 | 797 | 95.6 |
| Month 12 | 84 | 10.7 | 703 | 89.3 | 74 | 9.5 | 706 | 90.5 | 84 | 10.5 | 716 | 89.5 |
| Month 18 | 121 | 15.9 | 639 | 84.1 | 101 | 13.5 | 645 | 86.5 | 124 | 16.1 | 648 | 83.9 |
| Month 24 | 168 | 23.0 | 564 | 77.0 | 153 | 21.3 | 567 | 78.8 | 162 | 21.7 | 585 | 78.3 |
| | | | | | | | | | | | | |
| Month 30 | 201 | 28.4 | 506 | 71.6 | 177 | 25.4 | 521 | 74.6 | 197 | 26.9 | 535 | 73.1 |
| Month 36 | 233 | 34.9 | 434 | 65.1 | 203 | 31.0 | 451 | 69.0 | 236 | 33.6 | 467 | 66.4 |
| Month 42 | 259 | 45.8 | 306 | 54.2 | 221 | 41.1 | 317 | 58.9 | 257 | 43.1 | 339 | 56.9 |
| Month 48 | 272 | 57.7 | 199 | 42.3 | 226 | 52.0 | 209 | 48.0 | 276 | 56.9 | 209 | 43.1 |

AA = Anecortave Acetate

## Secondary Outcome Measure

**Proportion of Patients who Maintained Vision (< 15-Letter Loss) (Intent-to-Treat Data)**

| | AA 15 mg | | | | AA 30 mg | | | | Sham AA vehicle | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | < 15-Letter Loss | | ≥ 15-Letter Loss | | < 15-Letter Loss | | ≥ 15-Letter Loss | | < 15-Letter Loss | | ≥ 15-Letter Loss | |
| | N | % | N | % | N | % | N | % | N | % | N | % |
| Month 6 | 810 | 98.7 | 11 | 1.3 | 803 | 97.2 | 23 | 2.8 | 816 | 97.7 | 19 | 2.3 |
| Month 12 | 789 | 96.0 | 33 | 4.0 | 784 | 94.8 | 43 | 5.2 | 801 | 95.8 | 35 | 4.2 |
| Month 18 | 771 | 93.8 | 51 | 6.2 | 772 | 93.3 | 55 | 6.7 | 786 | 94.0 | 50 | 6.0 |
| Month 24 | 748 | 91.0 | 74 | 9.0 | 759 | 91.8 | 68 | 8.2 | 763 | 91.3 | 73 | 8.7 |
| | | | | | | | | | | | | |
| Month 30 | 732 | 89.1 | 90 | 10.9 | 744 | 90.0 | 83 | 10.0 | 752 | 90.0 | 84 | 10.0 |
| Month 36 | 714 | 86.9 | 108 | 13.1 | 729 | 88.1 | 98 | 11.9 | 734 | 87.8 | 102 | 12.2 |
| Month 42 | 698 | 84.9 | 124 | 15.1 | 724 | 87.5 | 103 | 12.5 | 719 | 86.0 | 117 | 14.0 |
| Month 48 | 689 | 83.8 | 133 | 16.2 | 712 | 86.1 | 115 | 13.9 | 714 | 85.4 | 122 | 14.6 |

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## Summary of Safety

Overall, based upon a review of AEs (deaths, serious AEs, AEs that led to discontinuation, and treatment-related events) and an assessment of ocular and systemic safety parameters, the administration of AA 15 mg or 30 mg by PJD at 6-month intervals for up to 48 months was safe and well tolerated in elderly patients 50 to 98 years of age with exudative AMD in 1 eye (non-study eye) and non-exudative AMD in the opposing eye (study eye) that was at risk for progressing to exudative AMD.

## Serious Adverse Events

Eight-hundred eleven (811) patients experienced serious adverse events (SAEs). All SAEs occurring in patients treated with Anecortave Acetate (15 mg or 30 mg) were assessed as unrelated to the use of test article.

## Other Adverse Events

**Frequency and Incidence of Adverse Reactions (Safety Analysis Set)**

| Treatment | AA 15 mg N = 866 | | AA 30 mg N = 862 | | Sham N = 868 | |
|---|---|---|---|---|---|---|
| **Coded Adverse Reaction** | N | % | N | % | N | % |
| *Cardiac disorders* | | | | | | |
| Myocardial Infarction | 0 | 0.0 | 0 | 0.0 | 1 | 0.1 |
| *Eye disorders* | | | | | | |
| Cataract | 1 | 0.1 | 2 | 0.2 | 3 | 0.3 |
| Visual Acuity Reduced | 5 | 0.6 | 1 | 0.1 | 1 | 0.1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Eyelid Oedema | 3 | 0.3 | 0 | 0.0 | 0 | 0.0 |
| Eyelid Ptosis | 1 | 0.1 | 1 | 0.1 | 1 | 0.1 |
| Macular Degeneration | 1 | 0.1 | 1 | 0.1 | 1 | 0.1 |
| Conjunctivitis | 1 | 0.1 | 1 | 0.1 | 0 | 0.0 |
| Foreign Body Sensation In Eyes | 1 | 0.1 | 1 | 0.1 | 0 | 0.0 |
| Ocular Hyperaemia | 1 | 0.1 | 1 | 0.1 | 0 | 0.0 |
| Erythema Of Eyelid | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 |
| Eye Pain | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 |
| Vision Blurred | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 |
| Eye Discharge | 0 | 0.0 | 1 | 0.1 | 1 | 0.1 |
| Eye Irritation | 0 | 0.0 | 1 | 0.1 | 1 | 0.1 |
| Pupils Unequal | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 |
| Visual Disturbance | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 |
| Vitreous Detachment | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 |
| Eye Swelling | 0 | 0.0 | 0 | 0.0 | 1 | 0.1 |
| *Infections and Infestations* | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Herpes Simplex Ophthalmic | 0 | 0.0 | 0 | 0.0 | 1 | 0.1 |
| *Injury, poisoning and procedural complications* | | | | | | |
| Conjunctival Scar | 2 | 0.2 | 1 | 0.1 | 0 | 0.0 |
| *Investigations* | | | | | | |
| Intraocular Pressure Decreased | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 |
| Intraocular Pressure Increased | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 |
| *Metabolism and nutrition disorders* | | | | | | |
| Type 2 Diabetes Mellitus | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 |

AA = Anecortave Acetate
Coded Adverse Reaction = MedDRA Preferred Term (version 11.0) presented by System Organ Class

## Other Relevant Findings

No other relevant findings to disclose.

## Date of Clinical Trial Report

15-Aug-2010