

Choroideremia Gene Therapy: Phase 2 Clinical Trial 36-Month Results and Overview

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Financial Disclosures

- **Biogen– Research Support**
- **Astellas– Paid Consultant**

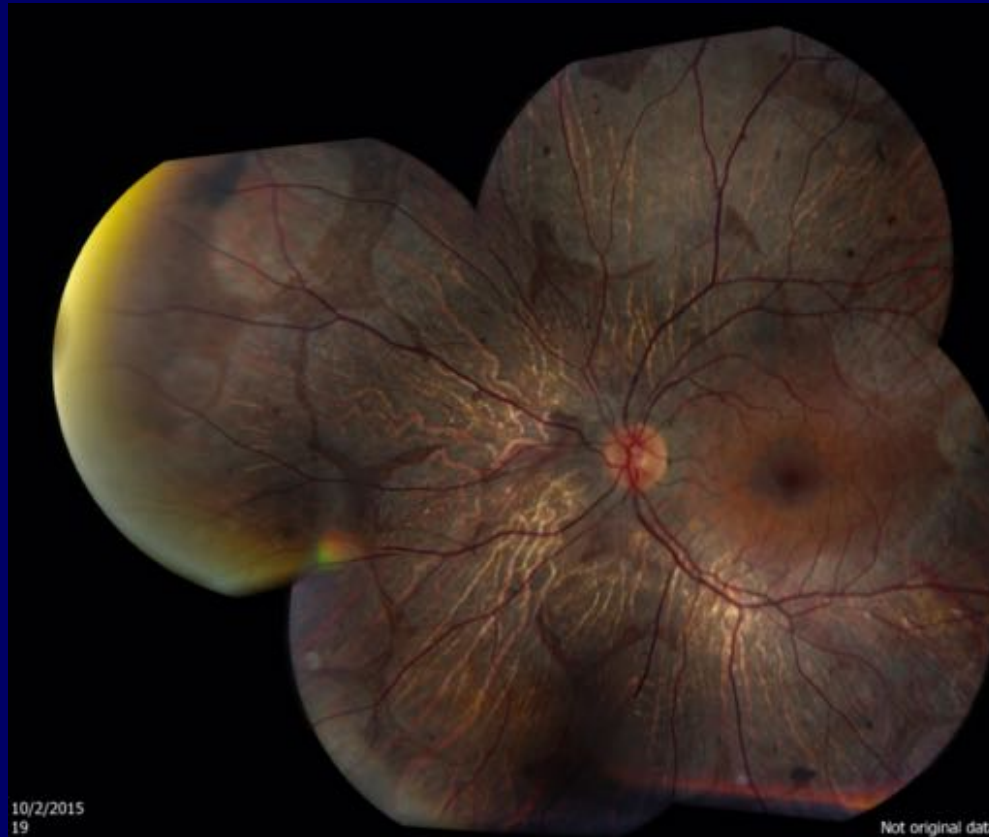
Choroideremia Gene Therapy AAV2-REP1 Phase 2

3 Year Results

Summary

- 10^{11} genome particles (high dose) is safe in bilateral sequential administration with few adverse events
- AAV-REP1 continues to have a good safety profile
- Visual acuity improvements occur in some patients shortly after therapy
- Microscope-integrated intraoperative OCT provides real-time feedback to guide accurate viral vector injection in these challenging cases

Choroideremia



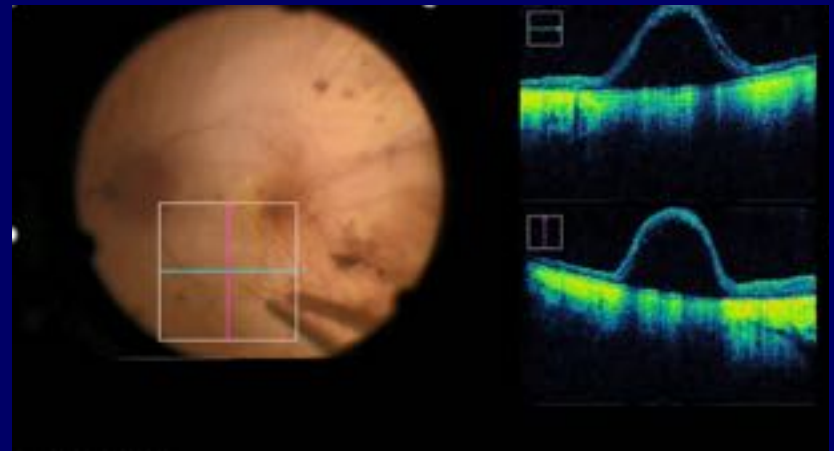
- X-linked recessive, primarily affecting males
- Gene encoding RAB escort protein 1 (REP1), mostly null mutations
- Gradual progressive loss of vision from chorioretinal degeneration starting from periphery toward fovea

Choroideremia Gene Therapy

- AAV2-REP1 vector
 - Chicken beta actin promoter
 - Woodchuck hepatitis viral post-translational regulatory element (WPRE), enhances expression
- To improve or maintain function of remaining RPE and photoreceptors
- Subretinal injection targeting fovea

Surgical Technique Edited by George A. Williams
Intraoperative Use of Microscope-Integrated
Optical Coherence Tomography for Subretinal
Gene Therapy Delivery

N. Z. Gregori, B.L. Lam, J.L. Davis
Retina, 2017, April 19



Choroideremia Gene Therapy

- Phase 2 Oxford (MacLaren)
- Phase 1-2 UPenn, Mass Eye & Ear
- Phase 2 – site initiated
 - Miami
 - Alberta
 - Germany
- Phase 2 multicenter sequential bilateral treatment (GEMNI – Biogen)
- Phase 3 multicenter randomized pivotal trial (STAR – Biogen)



Choroideremia Gene Therapy AAV2-REP1

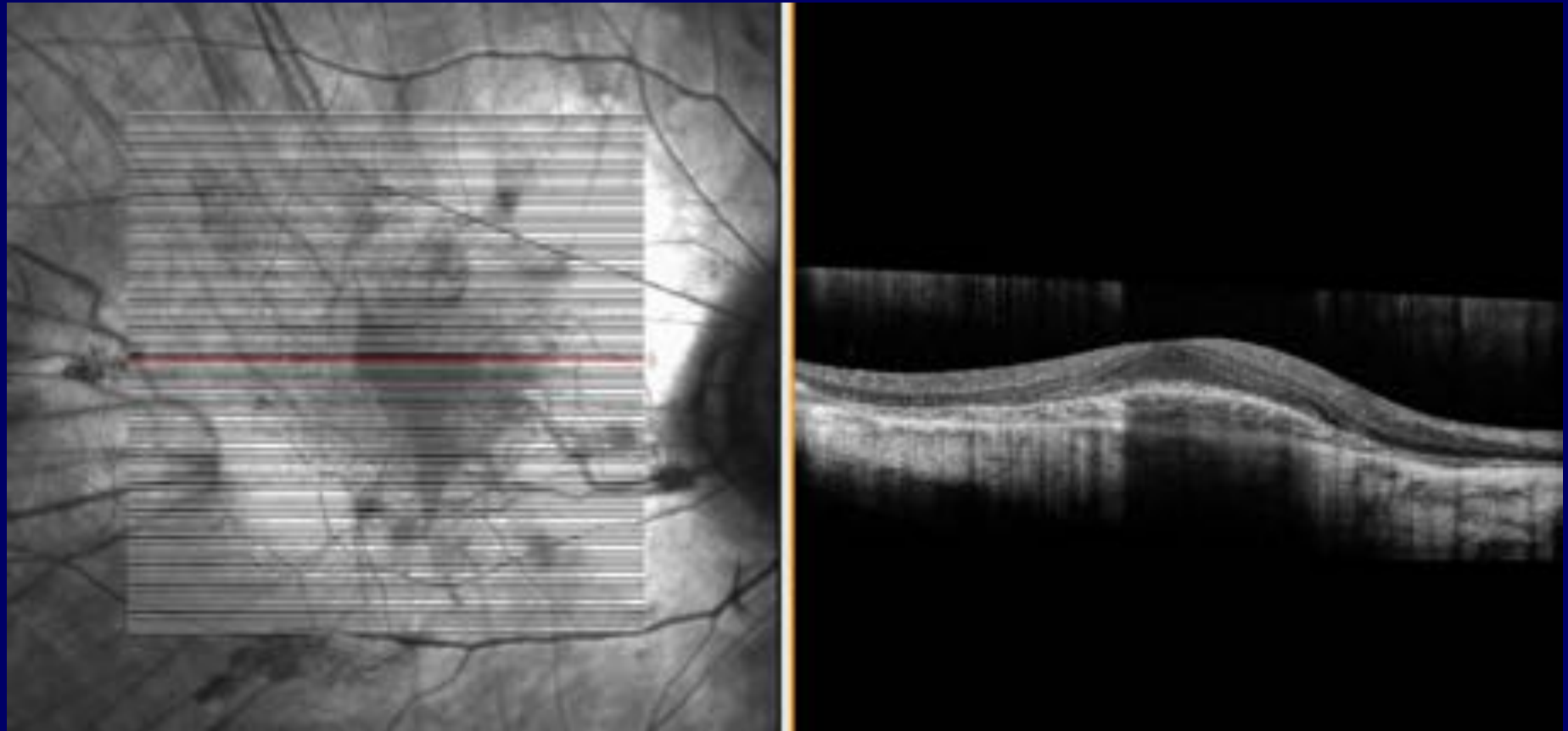
Open label Phase 2

Bascom Palmer Eye Institute

- 10^{11} genome particles (high dose)
- 100 ul subretinal, subfoveal
- Male > age 18 years, genetically proven choroideremia
- Active disease visible within macula region
- BCVA: 20/32 to 20/200
- Study period: to 2 years with further follow-up
- Primary endpoint: Visual Acuity
- *Patients were then recruited for 2nd eye surgery within the GEMINI study (Bilateral Phase 2 study)*



Subject Example



Choroideremia Gene Therapy AAV2-REP1 Phase 2 2 Year Results ETDRS VA Scores

| Patient No./ Age | Visual Acuity Baseline (ETDRS letter Score) | | Visual Acuity 1 Year (ETDRS letter Score) | | Visual Acuity 2 Year (ETDRS letter Score) | | Change in Letter Score Baseline to 2 Year | | Change in Letter Score Study Eye vs. Control Eye 2 Year |
|------------------|---|-------------|---|-------------|---|-------------|---|-------------|---|
| | Study Eye | Control Eye | Study Eye | Control Eye | Study Eye | Control Eye | Study Eye | Control Eye | |
| 501 50 yo | 65 | 81 | 69 | 79 | 70 | 80 | 5 | -1 | 6 |
| 502 53 yo | 61 | 77 | 71 | 78 | 71 | 77 | 10 | 0 | 10 |
| 503 49 yo | 56 | 69 | 54 | 71 | 56 | 71 | 0 | 2 | -2 |
| 504 72 yo | 58 | 77 | 58 | 75 | 57 | 75 | -1 | -2 | 1 |
| 505 50 yo | 75 | 78 | 78 | 84 | 77 | 82 | 2 | 4 | -2 |
| 506 32 yo | 77 | 80 | 80 | 80 | 79 | 80 | 2 | 0 | 2 |

AT 2 YEARS, 4 OUT OF 6 PATIENTS HAD SECOND EYE SURGERY

Choroideremia Gene Therapy AAV2-REP1 Phase 2
3 Year Results *IN THE FIRST TREATED EYE (n=6)*

ETDRS VA Score

| Patient No. | Visual Acuity Baseline (ETDRS letter score) | Visual Acuity 1 Year (ETDRS letter score) | Visual Acuity 2 Year (ETDRS letter score) | Visual Acuity 3 Year (ETDRS letter score) | Change in Letter Score Baseline to 3 Year, 1 st eye |
|-------------|--|--|--|--|--|
| 501 | 65 | 69 | 70 | 70 | 5 |
| 502 | 61 | 71 | 71 | 73 | 12 |
| 503 | 56 | 54 | 56 | 55 | -1 |
| 504 | 58 | 58 | 57 | 61 | 3 |
| 505 | 75 | 78 | 77 | 73 | -2 |
| 506 | 77 | 80 | 79 | 82 | 5 |

Choroideremia Gene Therapy AAV2-REP1 Phase 2
3 Year Results IN THE SECOND TREATED EYE (n=4)

ETDRS VA Score

| Patient No. | Visual Acuity Baseline (ETDRS letter score) | Visual Acuity 1 Year (ETDRS letter score) | Visual Acuity 2 Year (ETDRS letter score) | Visual Acuity 3 Year (ETDRS letter score) | Change in Letter Score Baseline to 3 Year |
|-------------|--|--|--|--|---|
| 502 | 77 | 78 | 77 | 80 | 3 |
| 504 | 77 | 75 | 75 | 78 | 1 |
| 505 | 78 | 84 | 82 | 80 | 2 |
| 506 | 80 | 80 | 80 | 78 | -2 |

Choroideremia Gene Therapy AAV2-REP1 Phase 2 3 Year Results

Adverse Events

| Adverse Events All Occurred in Treated Eye | Number of Subjects (Total n=6) | Severity | Start Date** | End Date** |
|---|--|-----------------|-------------------------|--------------------------------|
| Conjunctiva hemorrhage, edema | 6 | Mild | POD 1 | POD 26 - 28 |
| Anterior chamber cells | 5 | Mild | POD 1 | POD 7-13 |
| Vitreous cells | 2 | Mild | POD 1 | POD 6 |
| Subretinal fluid | 5 | Mild | POD 1 | 4 on POD 6 1 on POD 26 |
| Extrafoveal Macular retinal hole in area of non-functioning retina* | 2 | Mild | POD 1 | Not Resolved |
| Diplopia | 1 | Mild | POD 15 | POD 36 |
| Cataract (72 yo)*** | 1 | Moderate | POD 89 | POD 228 Cataract Surgery |

*In each cases, partial thickness thinning defect visible on pre-operative OCT

Choroideremia Gene Therapy AAV2-REP1 Phase 2 3 Year Results

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Choroideremia Gene Therapy AAV2-REP1 Phase 2 3 Year Results

Patient Visual Observations

| Patient Visual Observations in Study Eye | Patient No. | | | | | | Total Subjects |
|---|----------------|---|---|---|---|---|-------------------|
| | 1 | 2 | 3 | 4 | 5 | 6 | |
| Vision "clearer" or "sharper" | | x | x | | x | x | 4 |
| "Better contrast" | | x | | | | | 1 |
| "Sees color better" | | x | | | | x | 2 |
| "Night vision a little better" | | | | | | x | 1 |
| "Sees stars better" | | | | x | | | 1 |
| "Vision Brighter" | | | | | | x | 1 |
| "Light sensitivity" "or glare" | x | | | x | | | 2 |
| "Mild shade" | x | | x | x | | | 3 |
| "Increased visual noise" | | | x | | | | 1 |

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