AlphaCor: Device and Outcomes

Off-label use: AlphaCor is cleared for market by FDA, TGA and countries recognising the CE-mark but is sometimes used for off-label indications or in association with medications or devices not specifically approved for use in conjunction with the device.

Data as reported current to end April 2006

KPro Research at Lions Eye Institute, Perth

- Need for new generation KPro recognized
- Research into a keratoprosthetic device that would biointegrate began in 1989 under Traian Chirila
- Unique properties of PHEMA used to create a 2 part but unified device

Data as reported current to end April 2006

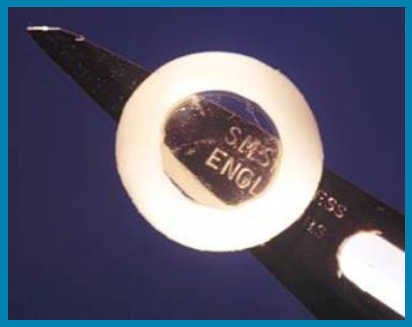
Concept: ‘Chirila Keratoprosthesis’

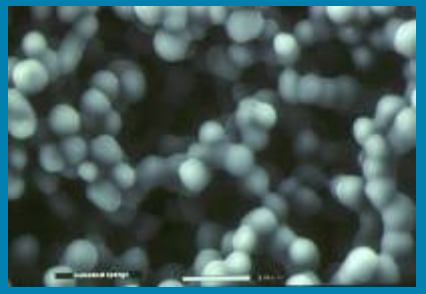
Core - non-rigid, transparent homogenous PHEMA

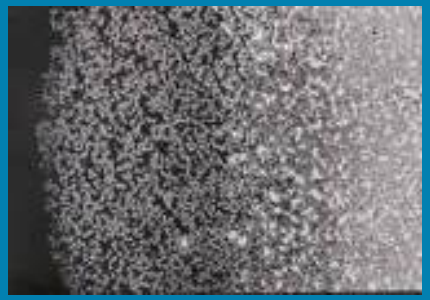
Skirt - porous, opaque, PHEMA

- allows biointegration

Fusion by a sequential interpenetrating polymer network (IPN)





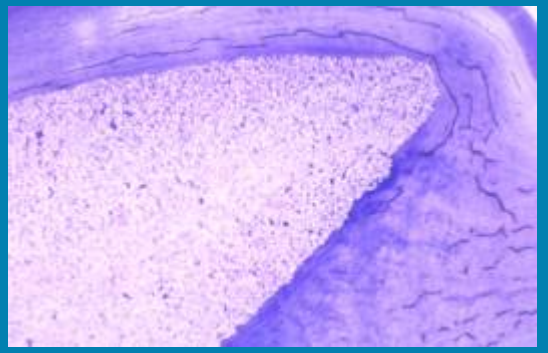


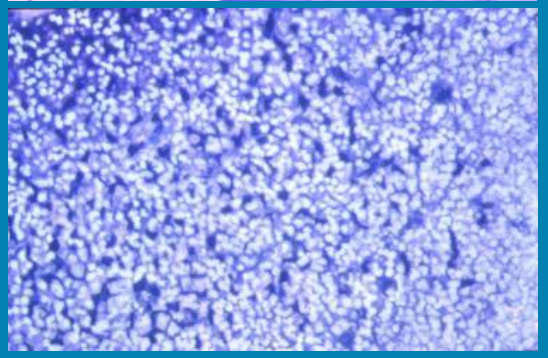
Data as reported current to end April 2006

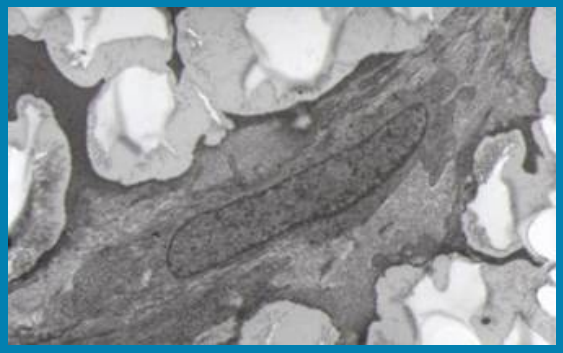
Studies - Biointegration

Implantation of porous hydrogels in central cornea of rabbit:

- No encapsulation
- Fibroblast invasion/turnover
- Collagen production by cells
- Stable capillaries
- Mild foreign body reaction
- No malignant cellular change







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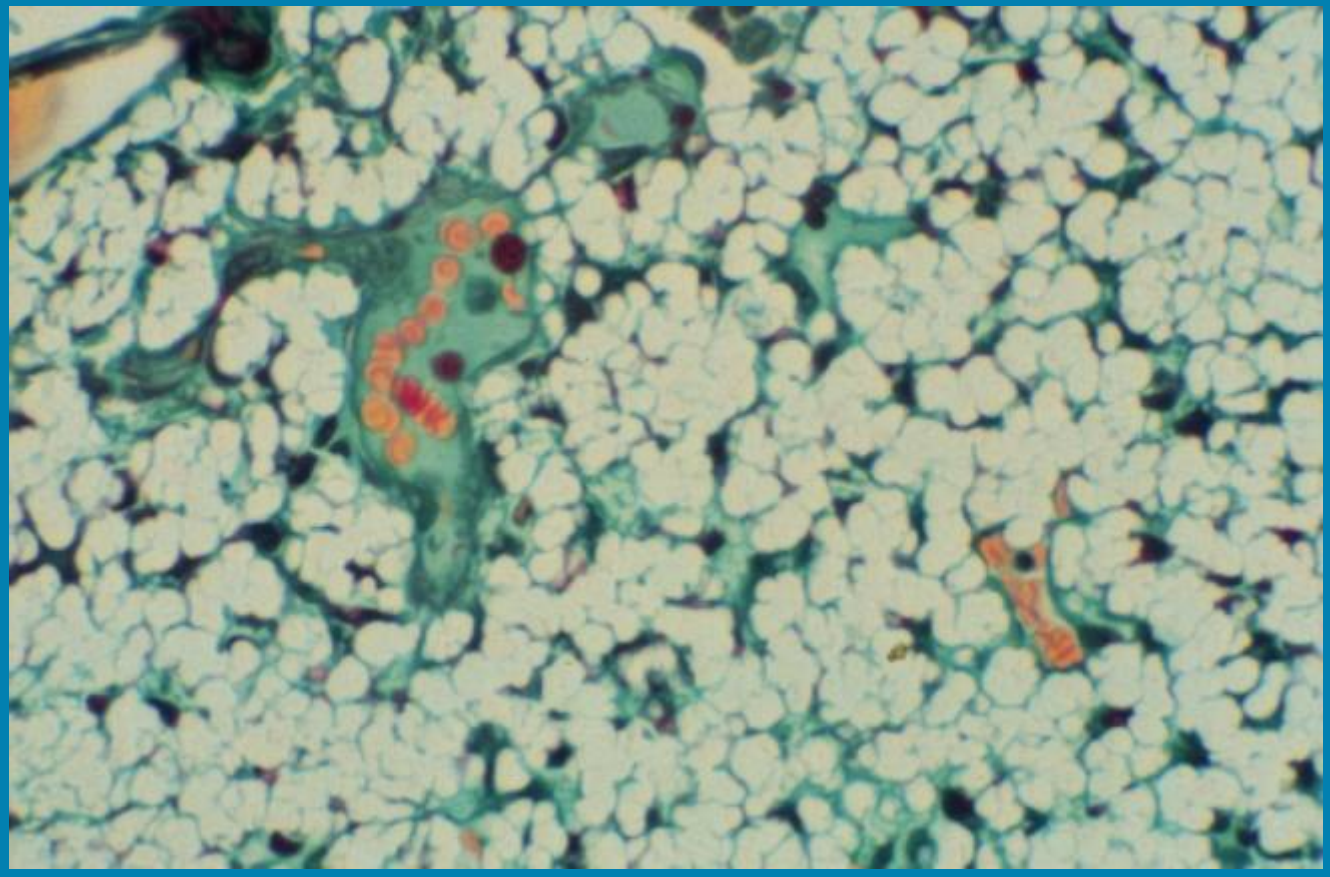


LM of skirt after biointegration

Data as reported current to end April 2006

Animal studies

1992-1998 Extensive animal implantations in over 250 rabbits and pigs. Devices maintained in place for up to 4 years. Firm integration occurred. Implantation technique evolved.

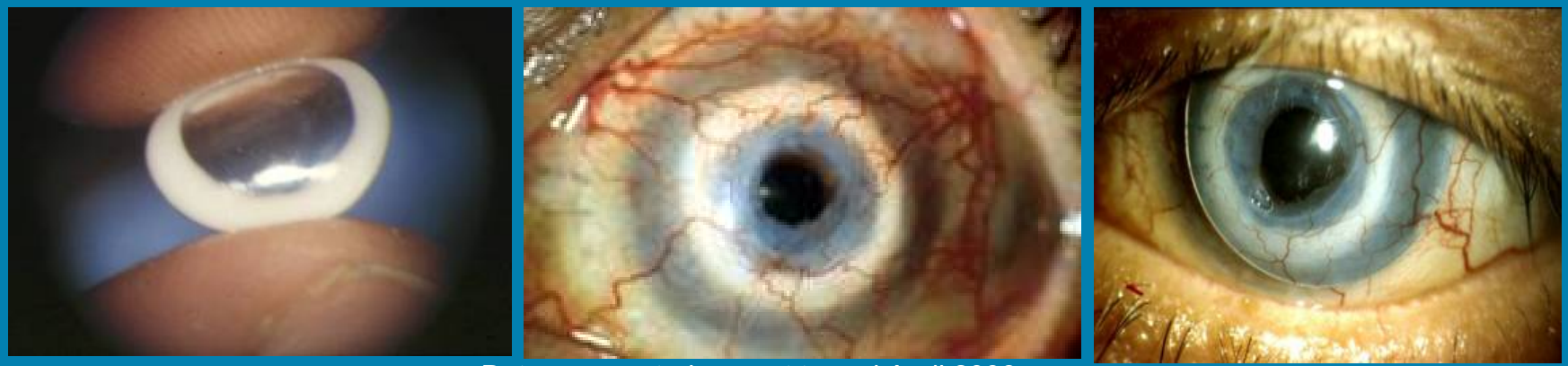
Final pre-human study in 24 rabbits: no extrusion, no infection, no retroprosthetic membranes, no deposits

Data as reported current to end April 2006

Human Clinical trials

Original Chirila Keratoprosthesis Type I was modified and evolved into AlphaCor

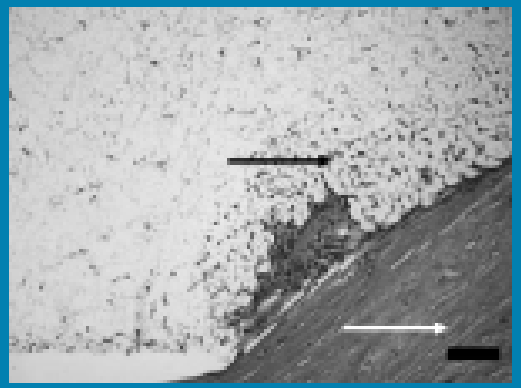
AlphaCor first implanted in humans in October 1998 in Perth, Australia



Data as reported current to end April 2006

Histologic findings of the AlphaCor skirt in humans are consistent with earlier animal studies.

- Biointegration by host fibroblastic cells, with collagen deposition occurs after AlphaCor implantation in humans.
- In cases in which stromal melting had occurred, biointegration is seen to be reduced.
- Preoperative vascularization appears not to be required for AlphaCor biointegration.



Hicks CR, Werner L, Vijayasekaran S, Mamalis N, Apple MD. Histology of AlphaCor skirts: evaluation of biointegration. *Cornea* 2005; 24: 933-940

Data as reported current to end April 2006

AlphaCor

Diameter : 7.0mm

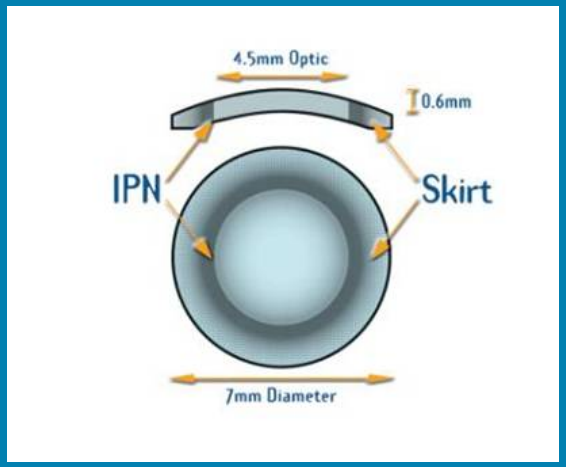
Two powers available:
Standard (AlphaCor-P) Aphakic (AlphaCor-A)

Implanted within the corneal plane

No routine iridectomy, vitrectomy, lensectomy or glaucoma surgery

Post-op IOP measurement possible

Procedure ‘reversible’ if necessary without loss of eye



Data as reported current to end April 2006

AlphaCor:
Trials and ongoing evaluation

1st 10 patients, first year – no complications

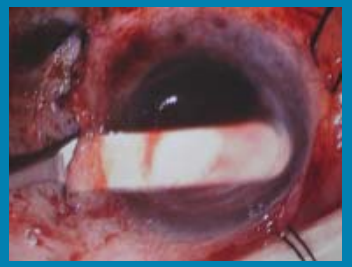
Complications reported over learning curve period and risk/protective factors identified

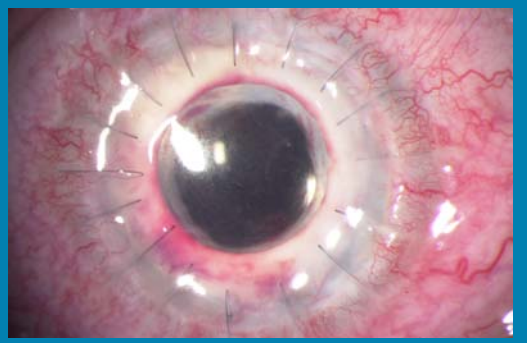
Established detailed data registry for ongoing data collection and analysis

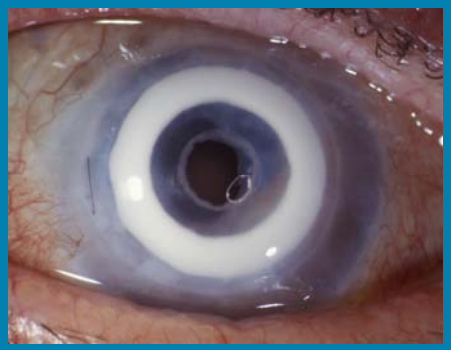
Data as reported current to end April 2006

AlphaCor:
Trials and ongoing evaluation

- Surgical technique evolving and simplified.
- Lamellar pocket from limbus, or within old PK only, trephined posteriorly before AlphaCor positioned. Anterior tissue removed after 3 months.
- Gunderson flap not usually required.
- Bandage lens wear common.
- Topical medroxyprogesterone 1% and topical antibiotic is standard postoperative regime.







Data as reported current to end April 2006

AlphaCor Data Overview

- Formal pre-regulatory approval trial N = 46
- Post-approval voluntary participation in database, 100% of N = 285 cases entered
- 88 surgeons participating in 11 countries
- Total 331 devices implanted
- 5 patients (1.5%) have died with device *in situ;* data censored

Data as reported current to end April 2006

Case Overview

- 70.1 % cases in USA
- Follow-up *in situ*
  - Mean = 16.3 months
  - Median = 14.0 months
  - Maximum = 7.5 years
- Represents 450 patient-years experience

Data as reported current to end April 2006

Pre-AlphaCor Histories

- Mean 2.4 prior failed grafts (0 (11.8%) – 13)
- Includes original pathologies:
  - 130 (39.3%) BK
  - 76 (23.0%) trauma/chemical burn
  - 36 (10.9%) bacterial/fungal keratitis
  - 30 (9.1%) LSCF including 29 (8.8%) aniridia
  - 23 (6.9%) HSV
  - 24 (7.3%) keratoconus and 1 (0.3%) keratoglobus
  - 20 (6.0%) Fuch's dystrophy
  - 7 (2.1%) silicone oil
  - 5 (1.5%) ICE
  - 5 (1.5%) Descemetocoele

Data as reported current to end April 2006

Glaucoma

- Pre-op glaucoma status
  - Pre-op glaucoma: 194 (58.6%)
  - Previous trabeculectomy: 33 (10.0%)
  - Previous shunt: 89 (26.9%)
  - Previous Laser: 3 (0.9%)
  - Glaucoma Rx prescribed: 157(48.8%)
- Post-op glaucoma status
  - de-novo glaucoma: 7 (2.1%)
  - Required shunt: 1 (0.3%)
  - Glaucoma Rx continued: 72 (21.8%)
  - Glaucoma Rx discontinued or not reported: 65 (19.6%)

Data as reported current to end April 2006

Lens Status

Pre-op:

- Aphakic: 64 (19.3%)
- Pseudophakic (any type): 204 (61.6%)
- Phakic: 63 (19.0%)

Combined Cataract/AlphaCor surgery in 16 cases

Cataract surgery does not affect AlphaCor retention (Chi^2)

Data as reported current to end April 2006

Serious Complications

- Eyes enucleated/eviscerated: 4 (1.2%)
  - Includes 2 cases endophthalmitis (both aqueous leakage and missed follow-up), 1 end-stage phthisical eye, and 1 recurrent stromal melt
  - 2 further cases culture-negative endophthalmitis/vitritis treated conservatively
- Rhegmatogenous RD: 2 (0.6%)

Any complication (minor-major): 45.9% cases

Data as reported current to end April 2006

Other Complications

Trends in Incidence

Complication	Contributory Causes	2003	2004	2005
Stromal melt	ocular surface, medication	24.7%	10.6%	11.4%
Optic Calcium	Steroid-B-blocker combo	5.7%	4.6%	2.6%
Optic- brown	Top. tetracyclines, smoking	6.6%	2.1%	0.4%
RPM	DM, HT, racial	8.6%	11.9%	5.1%
Poor integration	Peri-op complications	0%	3.1%	1.2%

Data as reported current to end April 2006

Risk Factors for Complications

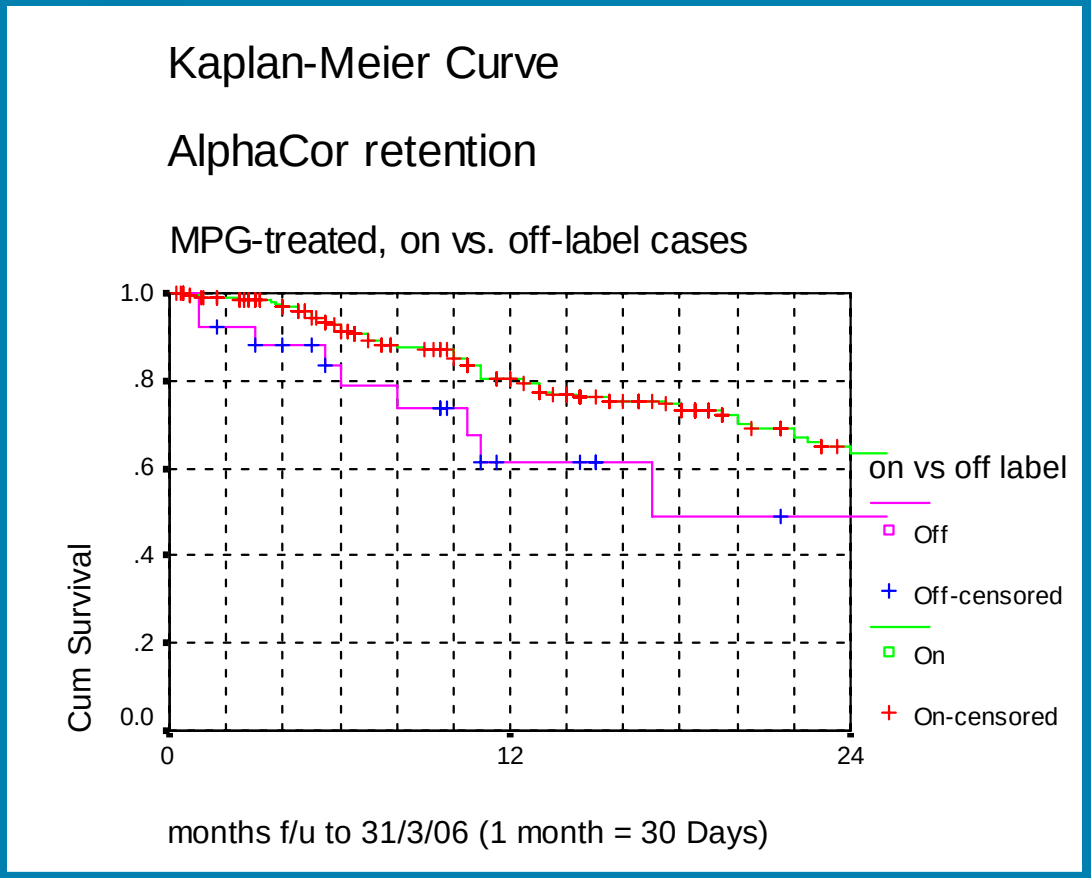
- Dry eye, diabetes, smoking, systemic hypertension and racial origin affected specific categories of complication and biological responses, as previously reported.
- Specific risk factors can be identified and used to guide patient selection and consent.
- Histological study provides evidence of biocompatibility and cellular reactions.

Data as reported current to end April 2006

Probability Retention

- P 6 mo S = 92%
- P 1-year S = 81%
- P 2-year S = 63%

- % all on-label post-trial devices *in situ* = 72.2%



Data as reported current to end April 2006

Safety Evaluation

- Eyes lost (evisceration/enucleation) = 4
- Eyes NPL with device *in situ* = 2 (because of dense recurrent RPM)
- Thus 6 eyes lost vision over 450 sum years follow-up
- Annual incidence/risk per eye 0.013

- Where device removal required
  - 18.6% device exchanged for a new one
  - 77.9% ‘reversed’ to PK (i.e. pre-AlphaCor status regained)
  - 3.5% device removed with globe

Data as reported current to end April 2006

Efficacy: Visual Acuity Outcomes

- Mean BCVA of last PK before failure = 20/300 (PL-20/70)
- Mean BCVA just before AlphaCor = HM
- Mean best BCVA after AlphaCor = 20/200 (PL-20/20)
- Significant improvement in vision after AlphaCor ($p < 0.001$)
- Mean BCVA after AlphaCor not different from mean BCVA of last PK before it failed ($p = 0.737$)**
- * all post-stage II cases included ** Paired Samples t-test

Data as reported current to end April 2006

Conclusions

- AlphaCor can restore full visual potential
- Low risk serious sight-threatening complications (loss of eye or de novo/progressed glaucoma)
- Overall fall in complication rate
- Reversible procedure able to improve vision where a graft would fail

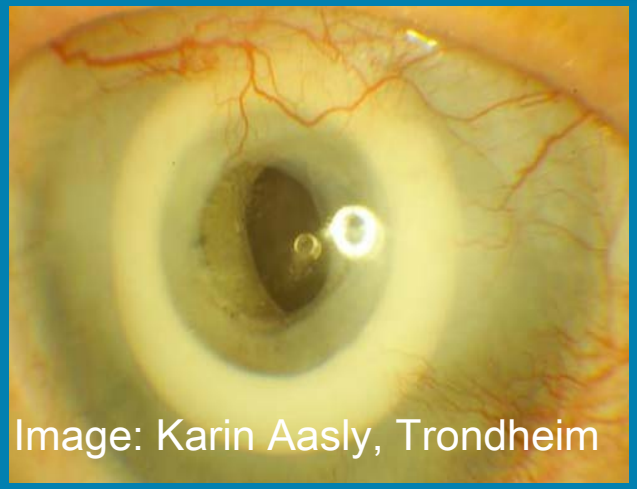


Image: Karin Aasly, Trondheim

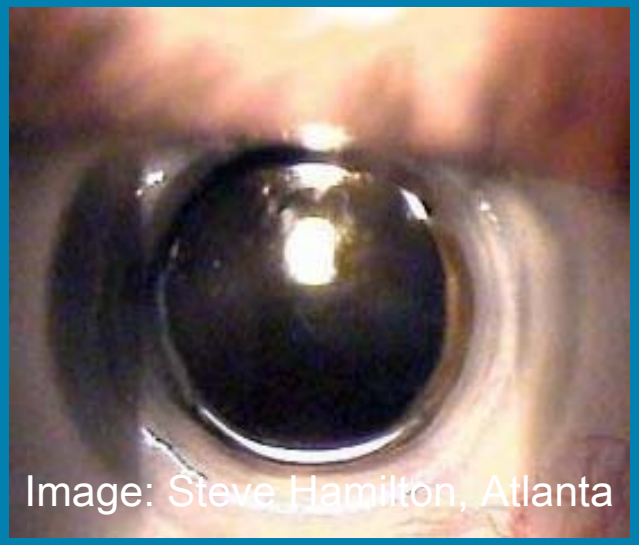


Image: Steve Hamilton, Atlanta

Data as reported current to end April 2006

The Scientific Advisory Board Gratefully Acknowledges Contributors of Data

Aasly K, Abel R, Afshari N, Akpek E, Aldave A, Aquavella J, Awwad S, Bleckmann H, Bobrow J, Bokosky J, Caparossi A, Caudill J, Channa P, Chen P, Chern K, Chodosh J, Cohen I, Cohen S, Conners M, Cowden J, *Crawford G*, Dart J, Daya S, Dhaliwal D, Downie N, Dunn S, Eguchi H, Eiferman R, Fulcher S, Gaster R, Geerling G, Gillette T, Goins K, **Gondhowiardjo T**, Goodwin L, Gorovoy M, Grabner G, Gritz D, Grutzmacher R, Gulani A, *Hamilton S*, Hardten D, Hirst L, Holland E, John T, Karbassi M, Katsev D, Kaufman H, Kim J, Lahner W, **Lam D**, Leahey A, Lundergan M, Macsai M, Mah F, Malecha M, Manche E, Mayers M, McCaa C, Moshifir M, Pangalinan R, Parker J, Pflugfelder S, *Price F*, Prosdocimo G, Raber I, Randleman B, Rapisarda A ,Rapuano C, Remejier L, Rodriguez L, Rosenwasser G, Rotkis W, *Rozsival P*, Silverstein S, **Snibson G**, Song J, *Stulting RD*, Sutphin J, **Sutton G**, *Taravella M*, Tauber J, *Tauber S*, **Tan D**, Tran U, Wang M

Honorary member Scientific Advisory Board
Clinical Investigator in Regulatory Trials
Member of AlphaCor Accreditation Faculty

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