

DMLA: une vue d'ensemble

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Disclosures

Consultant for:

- Allergan
- Bayer
- Novartis
- Roche
- Thea

En théorie

- Maculopathie liée à l'âge
- Atrophie géographique
- DMLA exsudative

DMLA atrophique

Définition et terminologies

Aspects cliniques

Examens complémentaires

Diagnostic différentiel

Traitements actuels

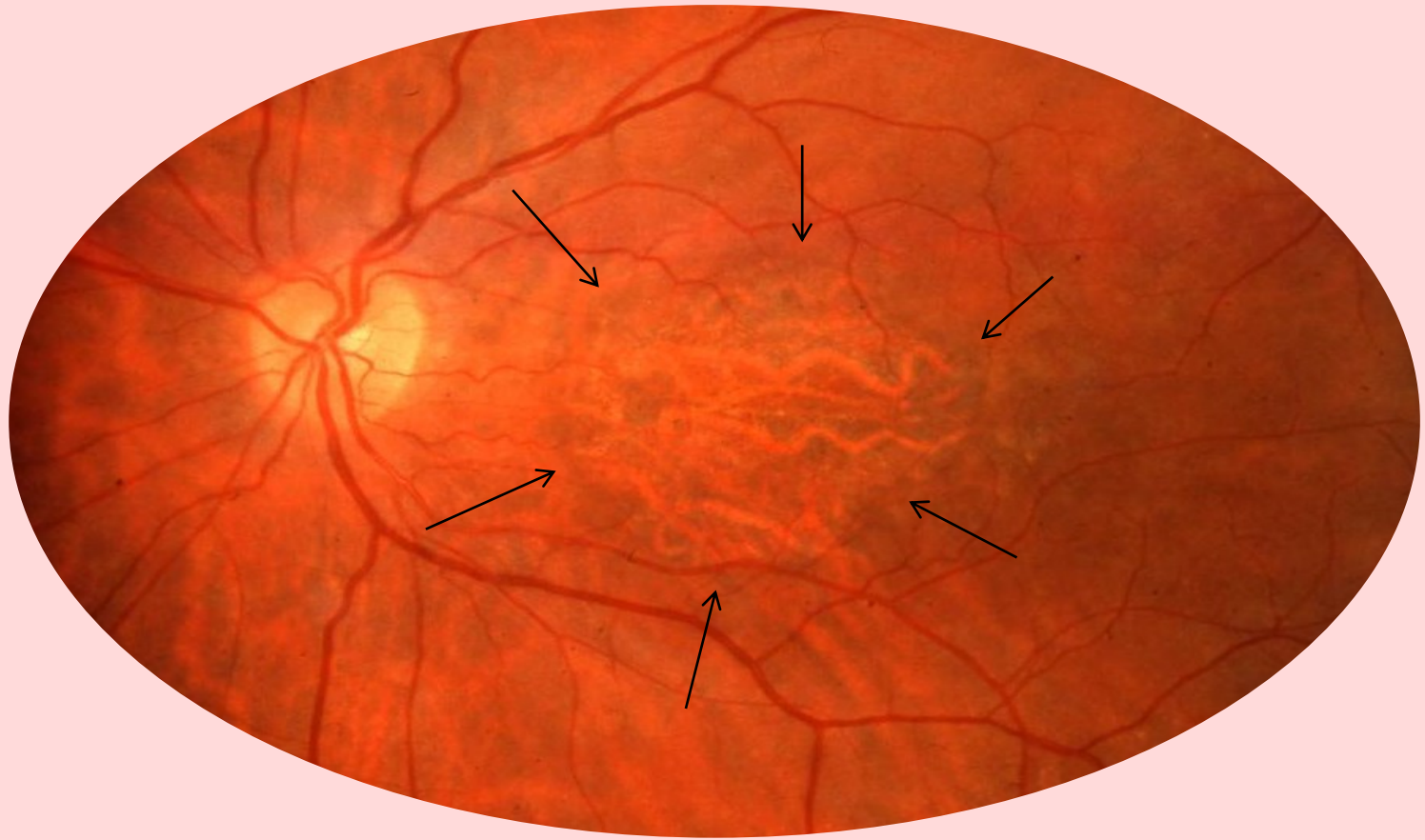
Traitements futurs

DMLA atrophique

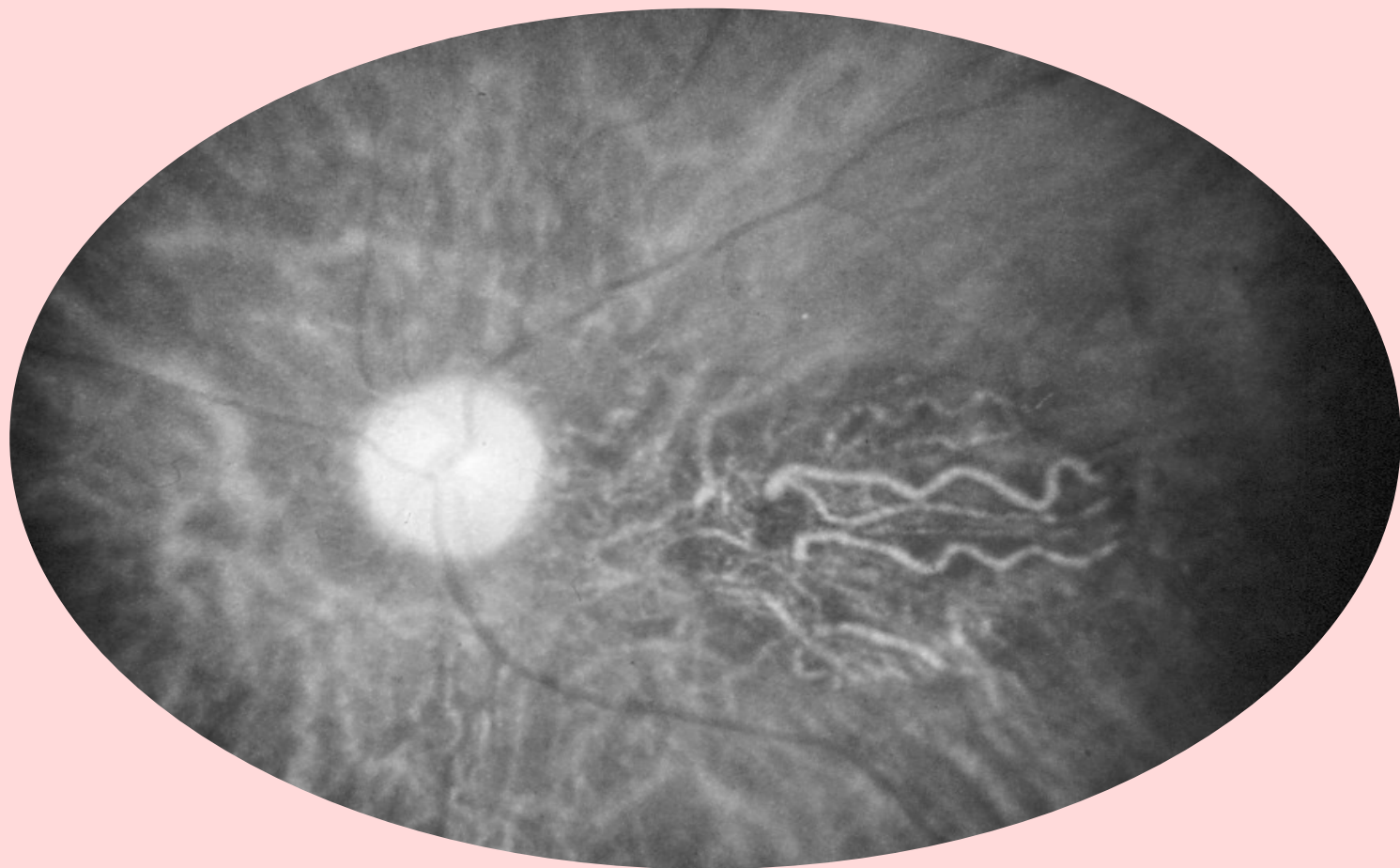
Histologie : disparition des cellules de L'EP
⇒ Disparition des photorécepteurs
Atrophie de la choriocapillaire

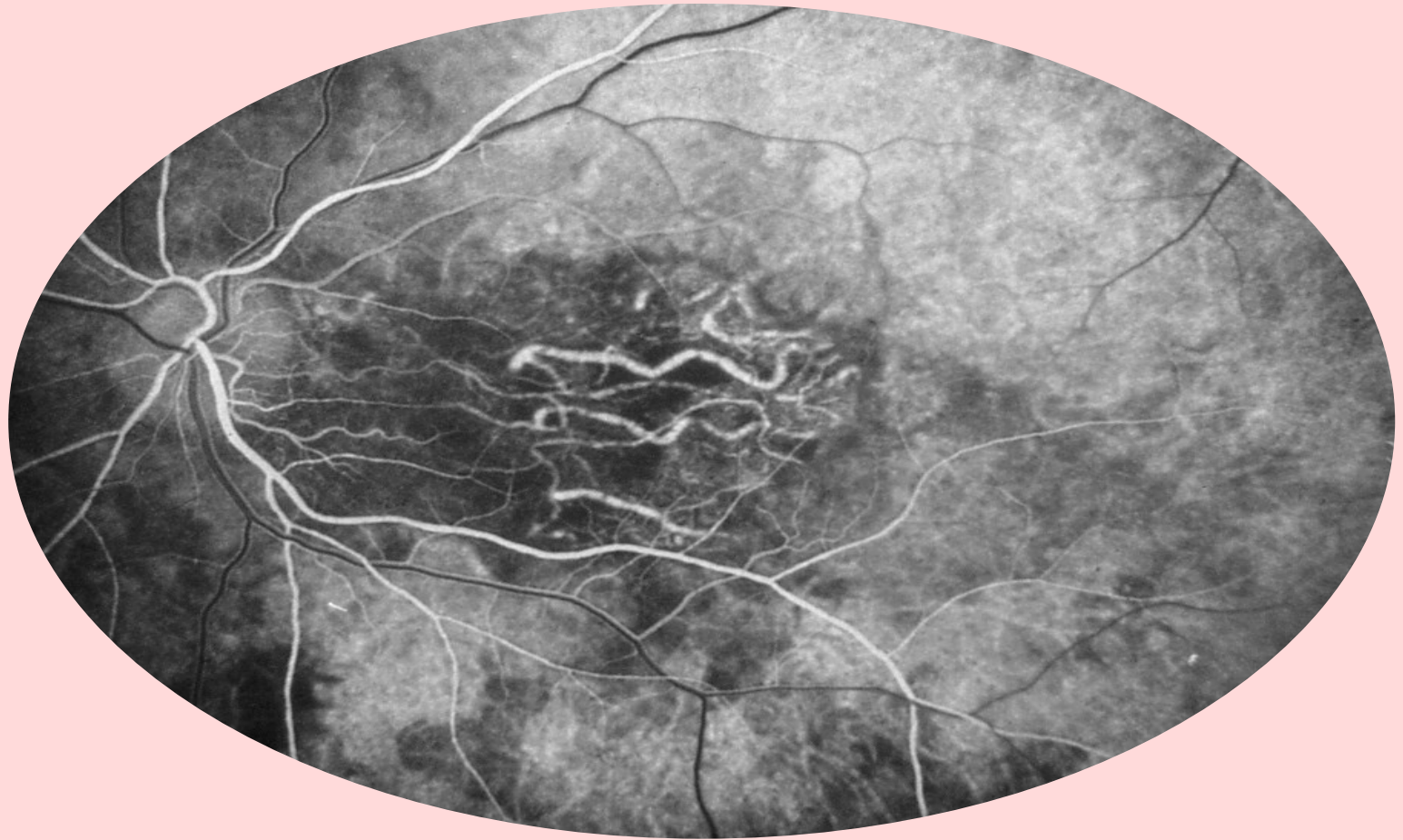
TERMINOLOGIES

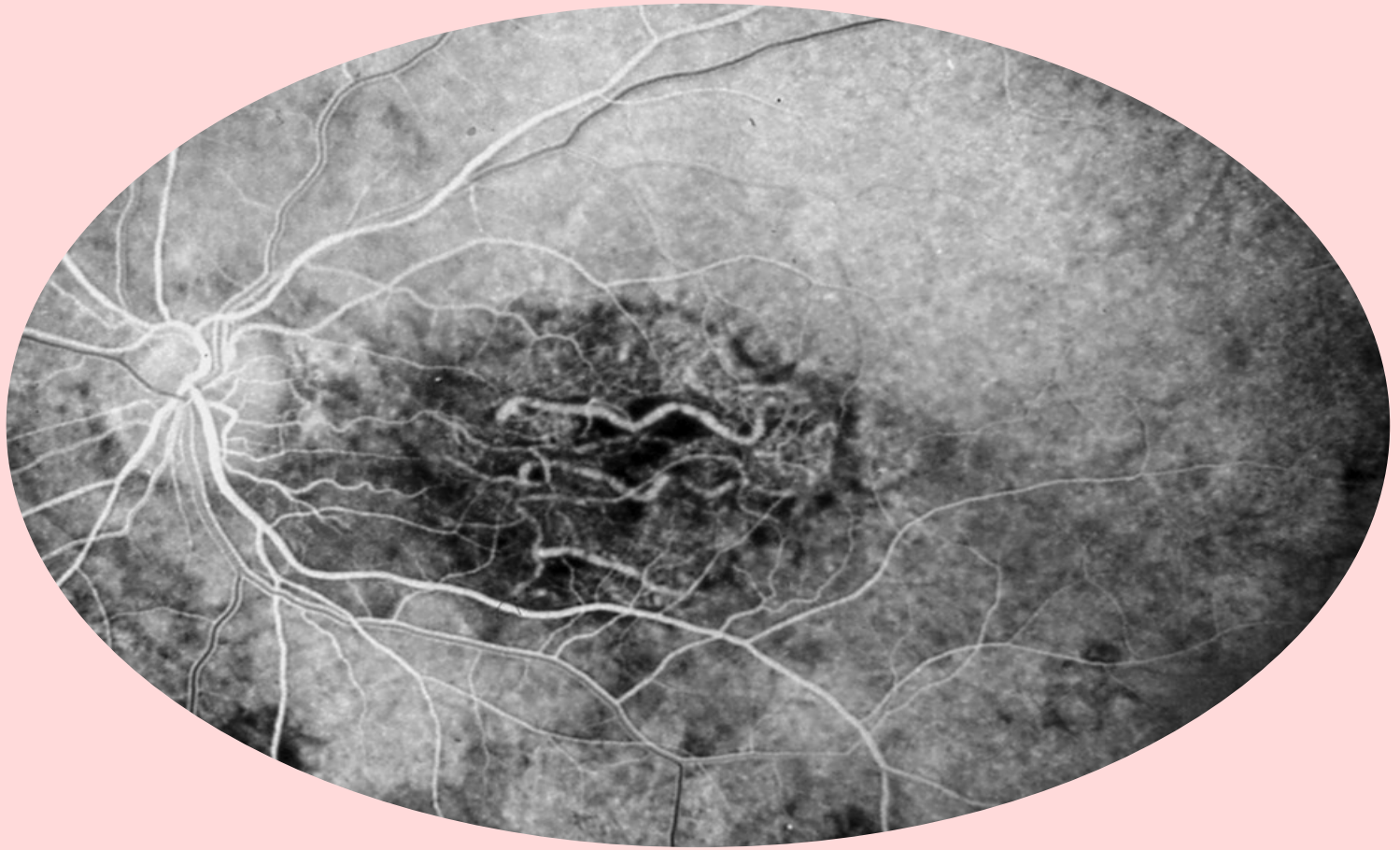
- DMLA atrophique
- **Atrophie géographique**
- Atrophie aréolaire
- Sclérose choroïdienne sénile
- (Sclérose aréolaire centrale : Formes héréditaires)

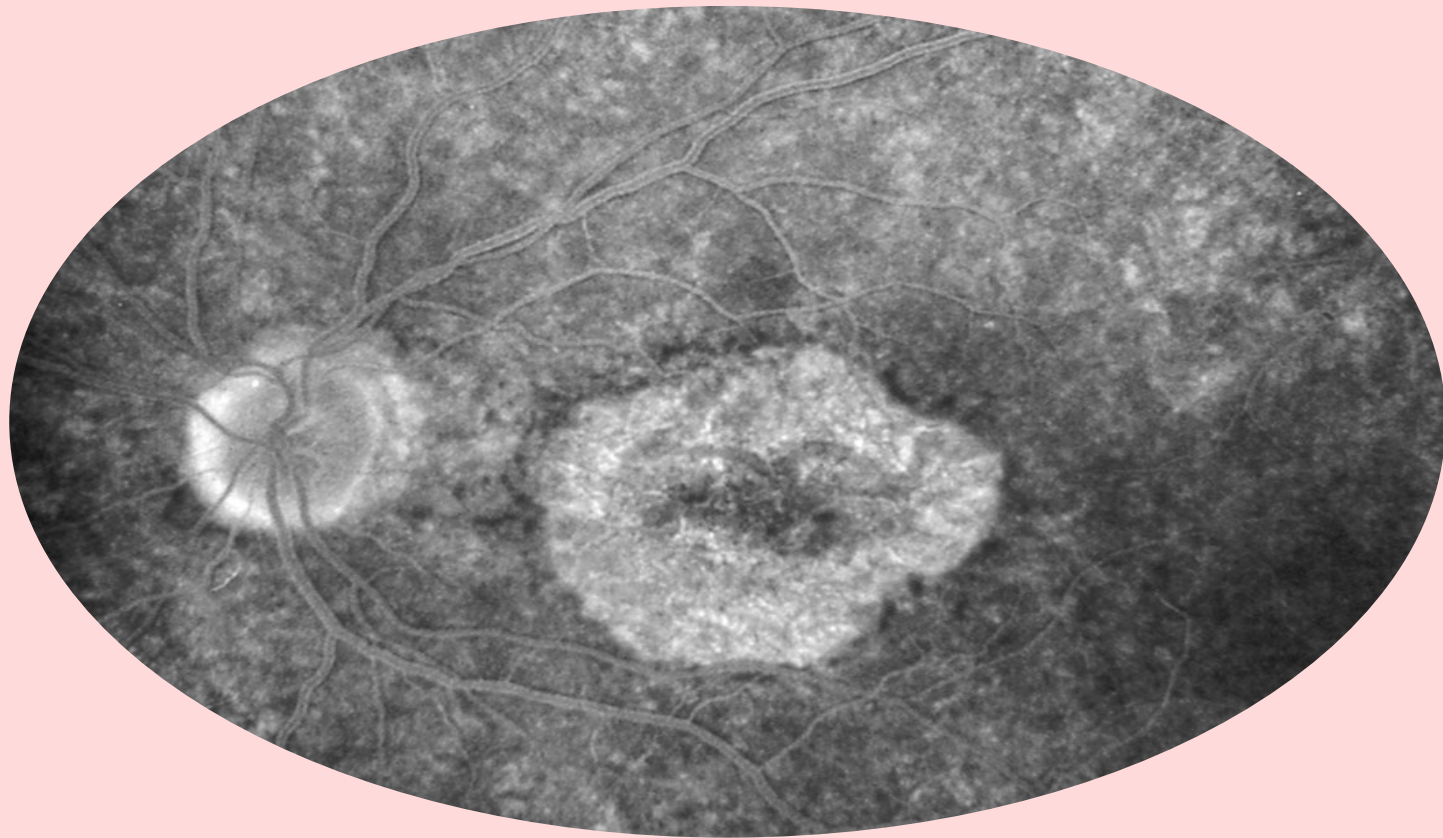


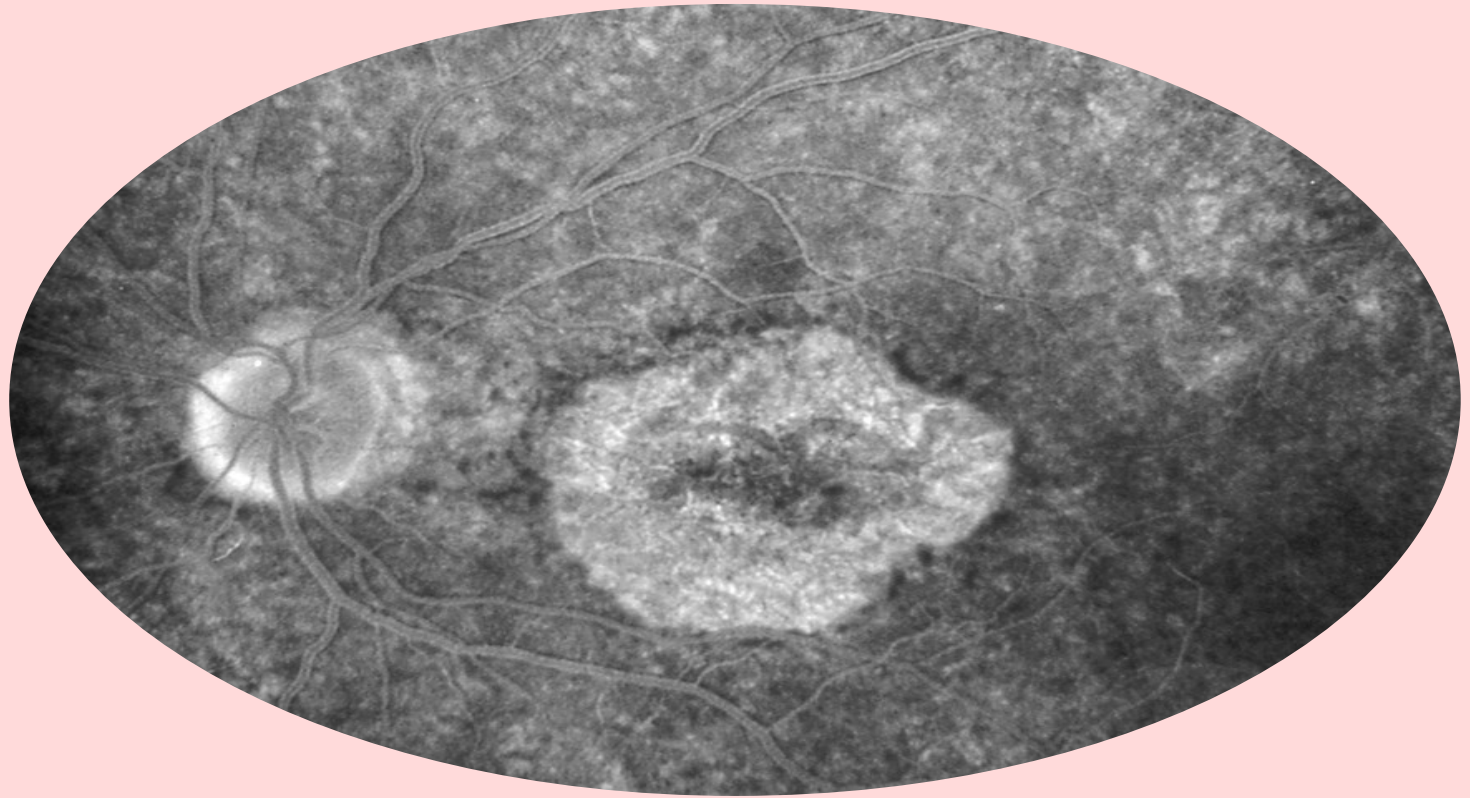
A une époque, toute DMLA avait une angiographie



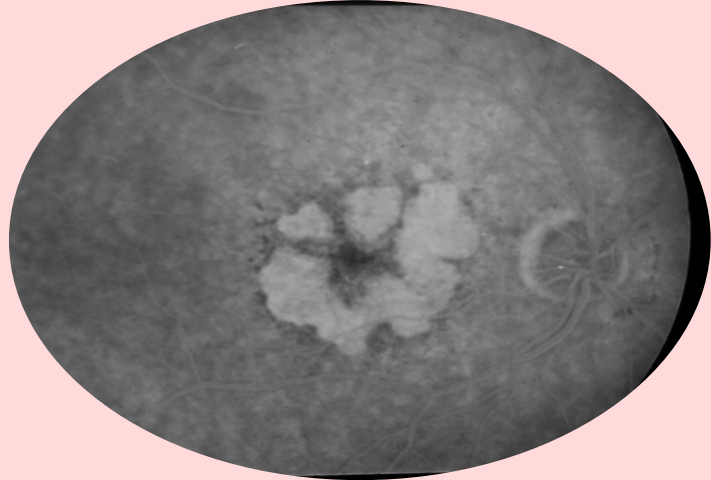
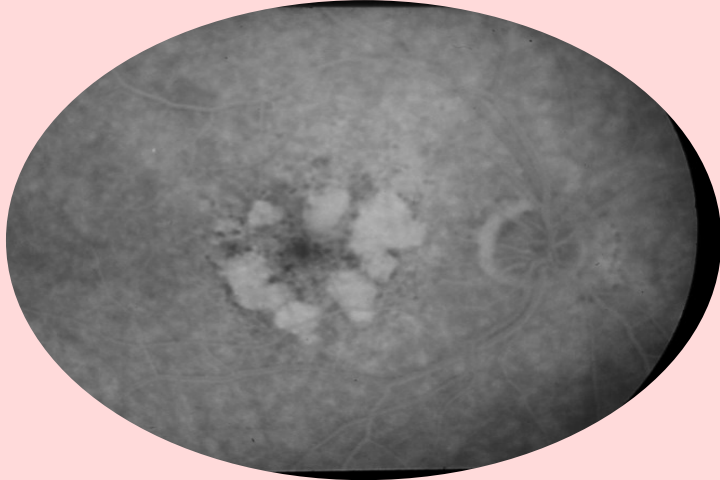
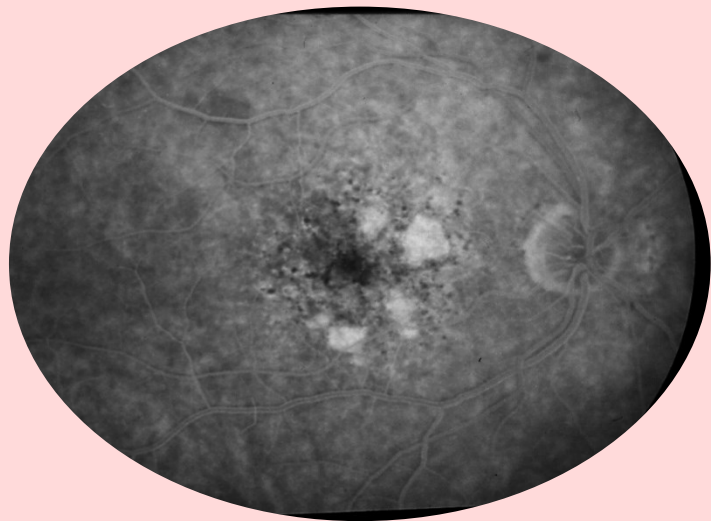
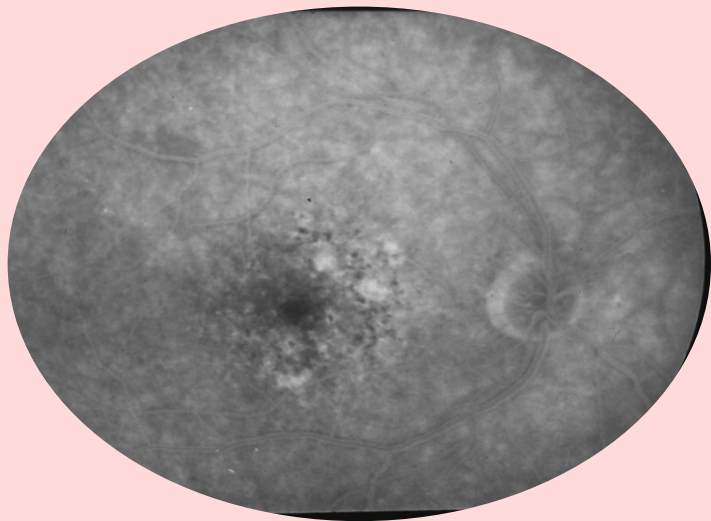


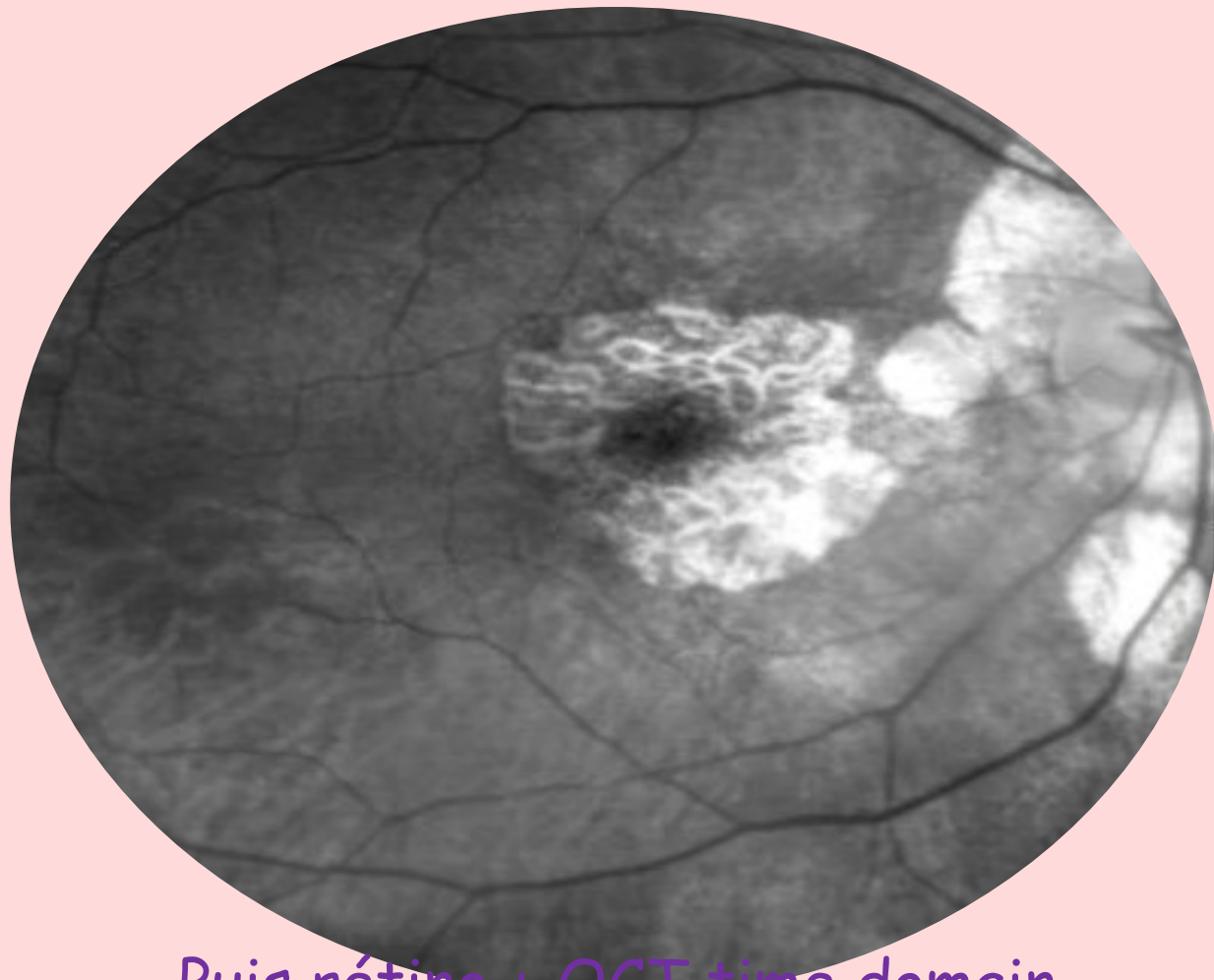




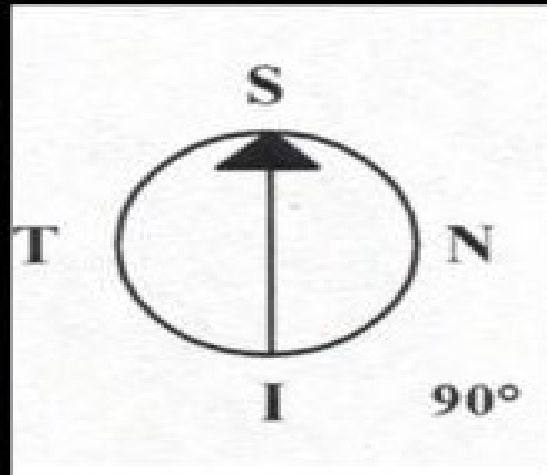


Effet Fenêtre: transmission de la fluorescence sclérale

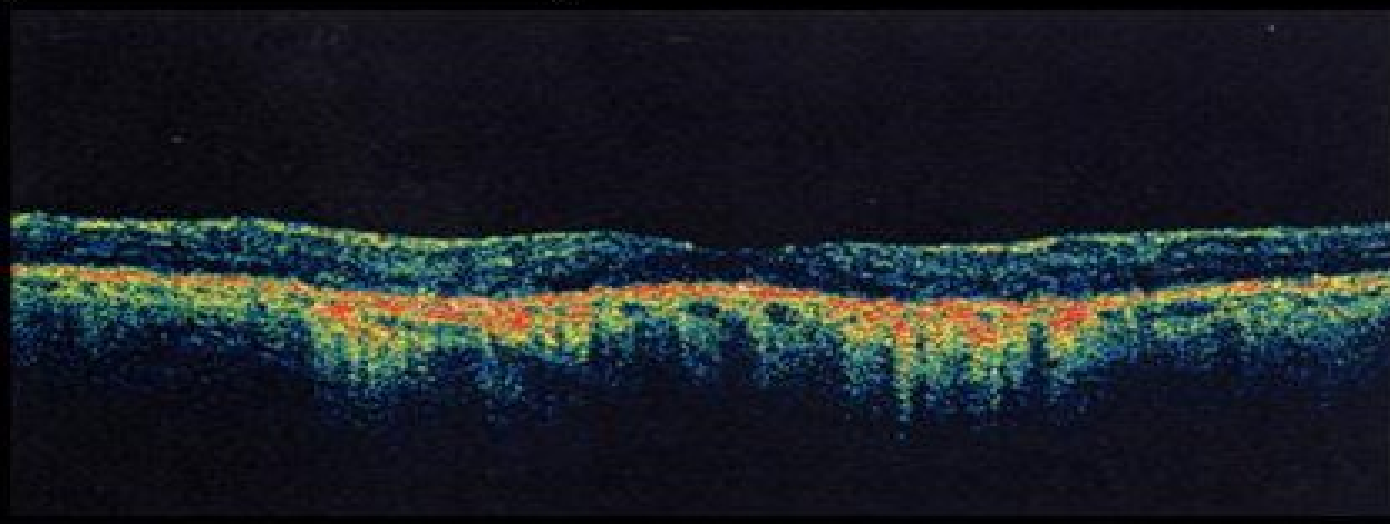
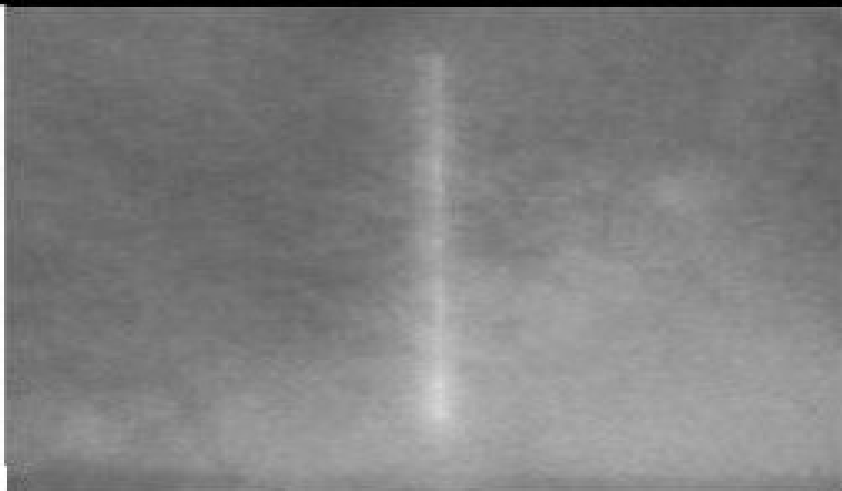


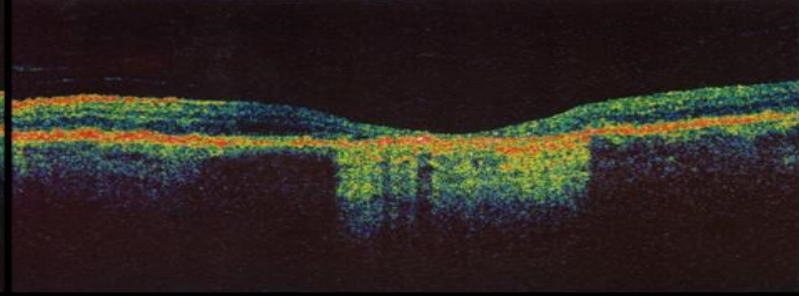
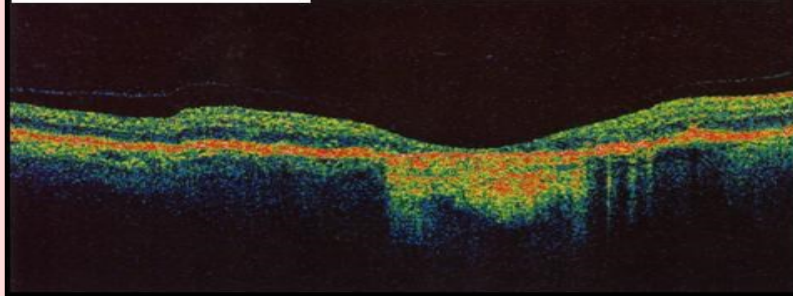
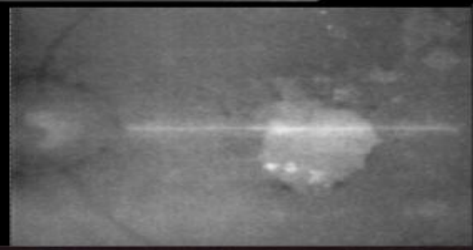
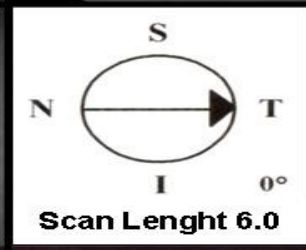
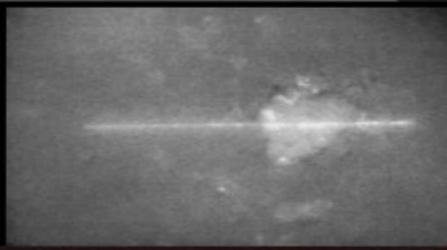
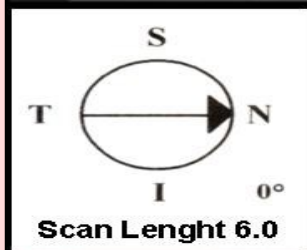
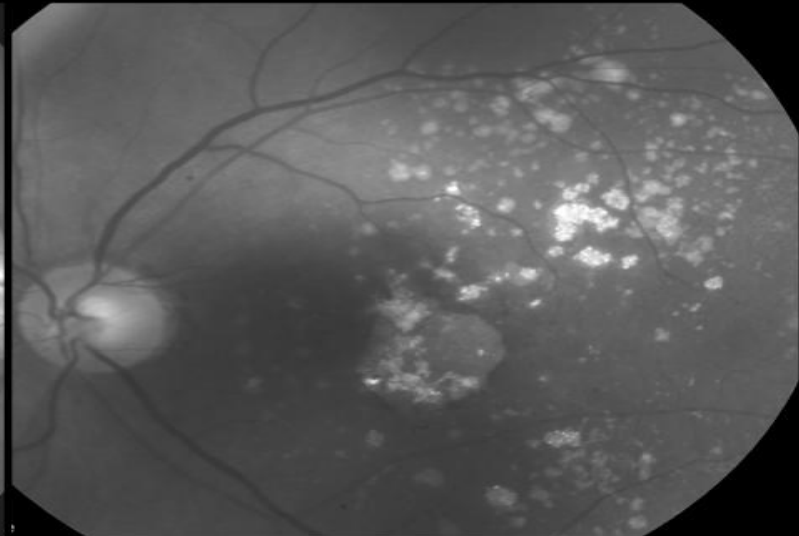
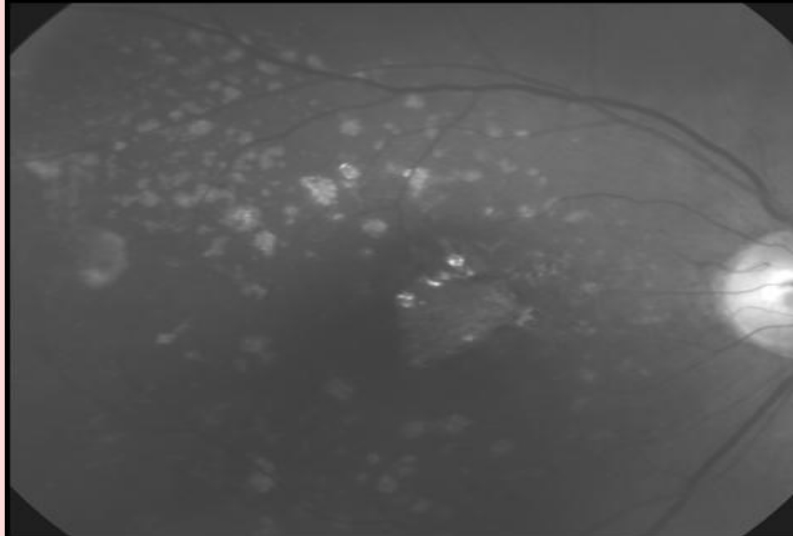


Puis rétino + OCT time domain



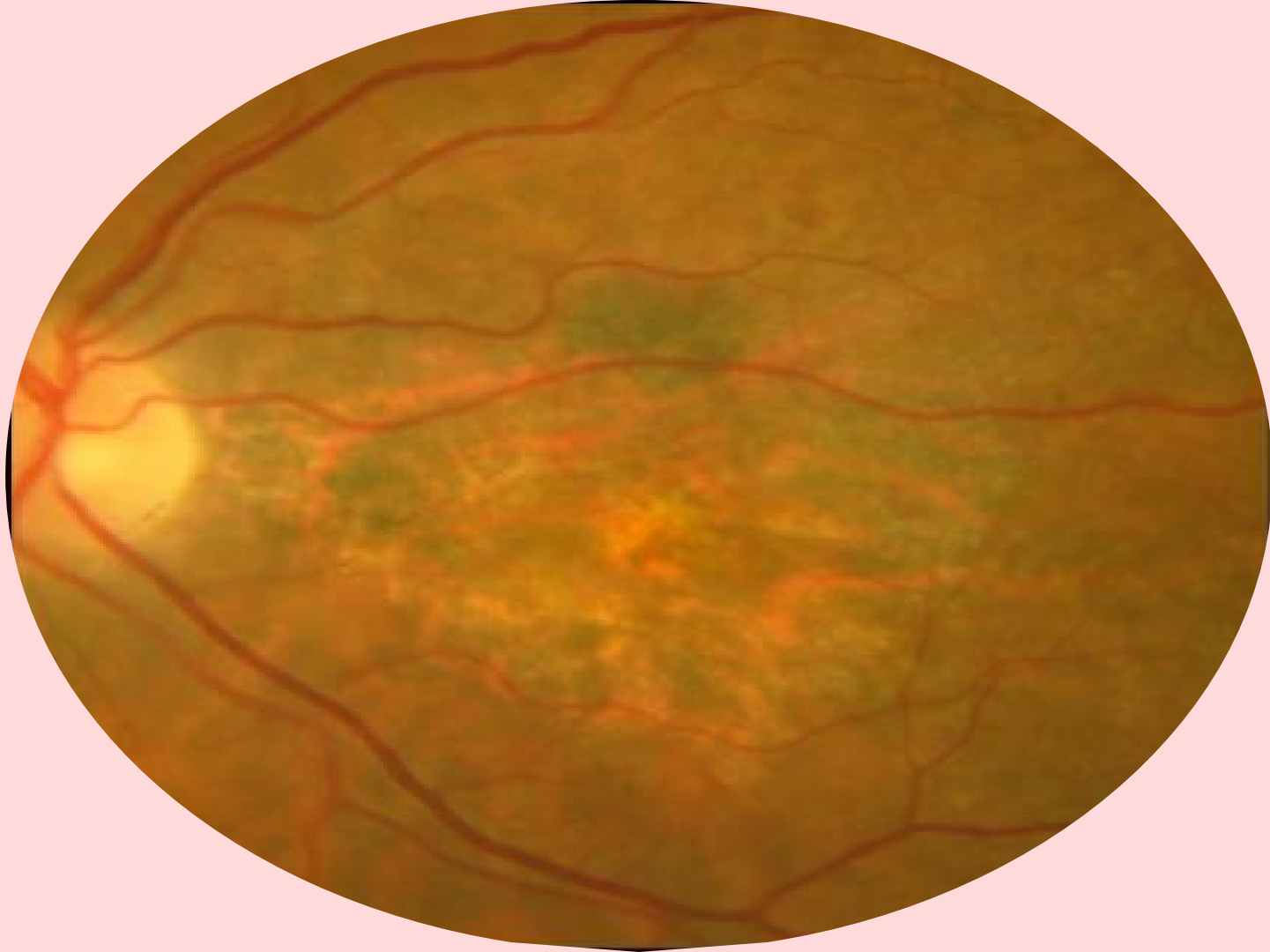
Scan Length 5.0

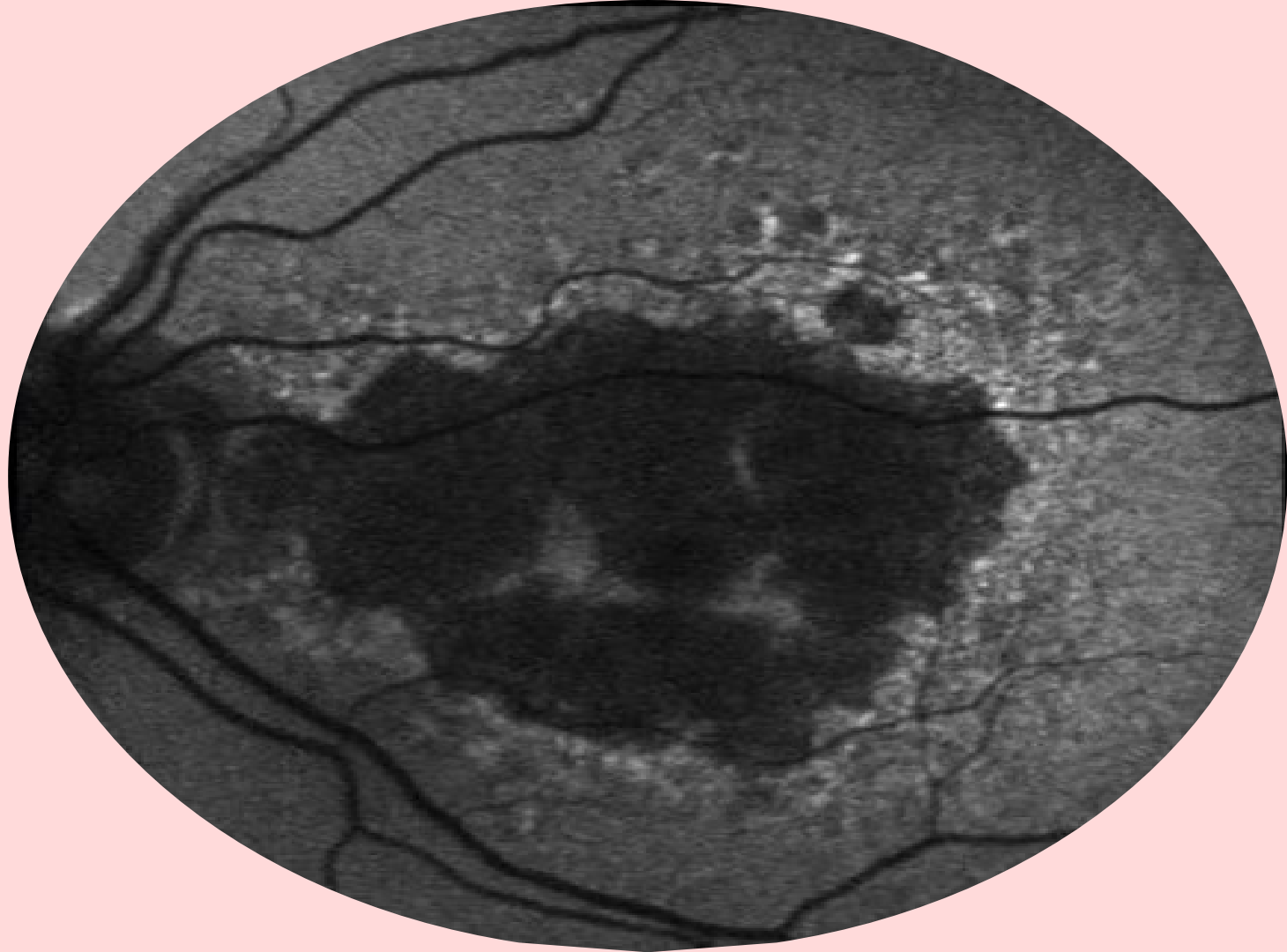




L'imagerie plus récente de l'atrophie géographique fait appel à

- l'autofluorescence du fond d'œil
- l'OCT spectral-domain





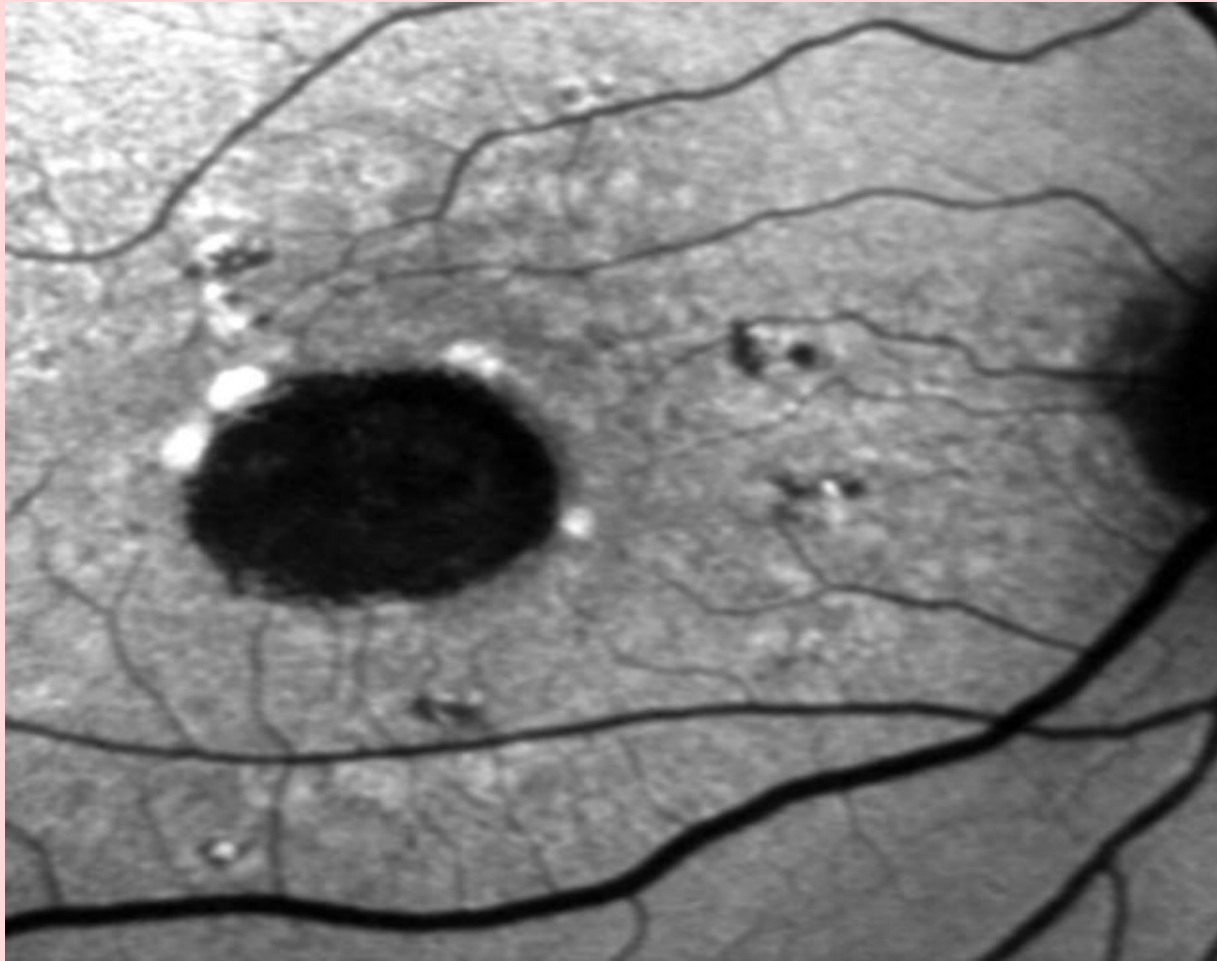


Documenter l'histoire naturelle de l'atrophie géographique et tester les nouvelles thérapeutiques

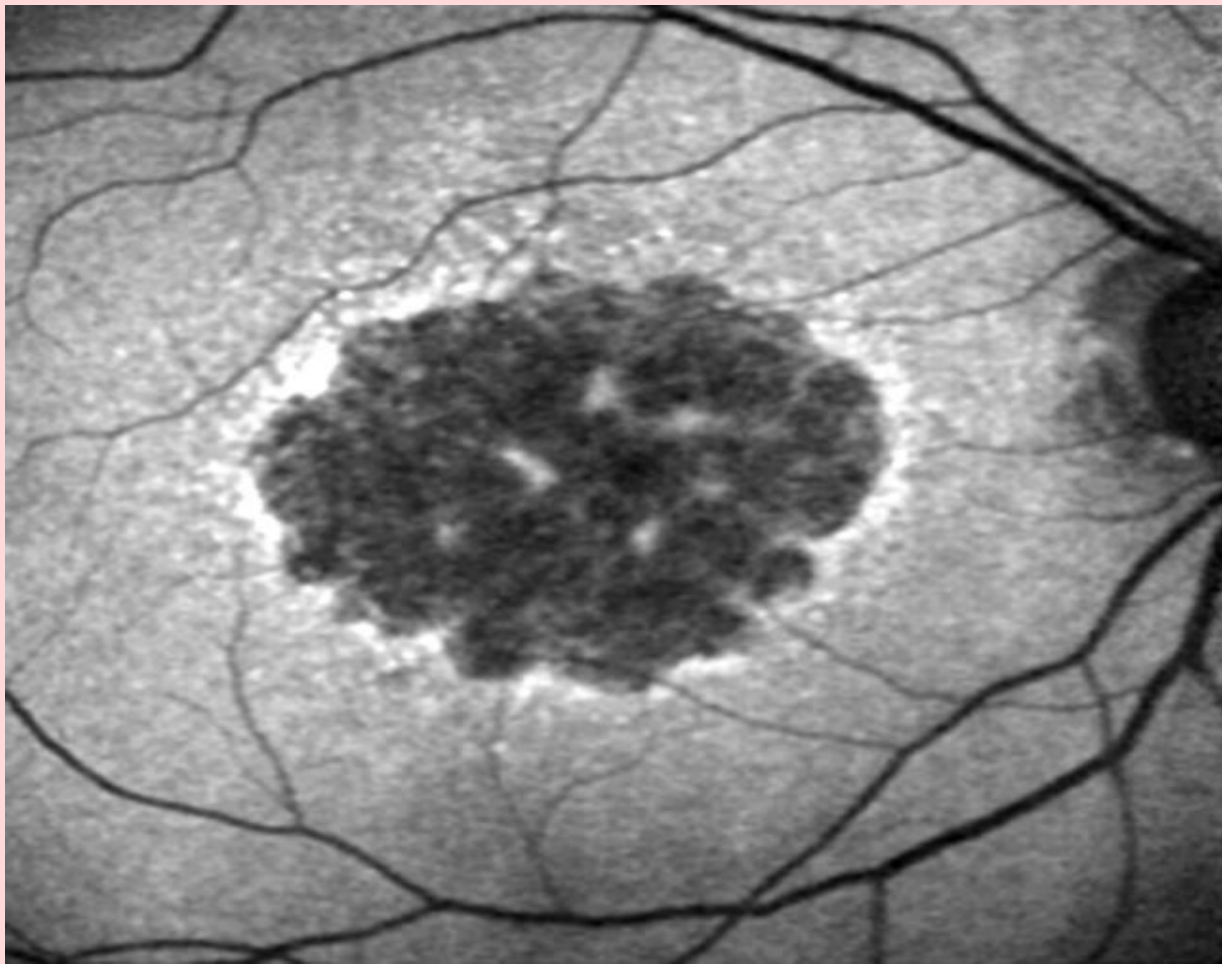




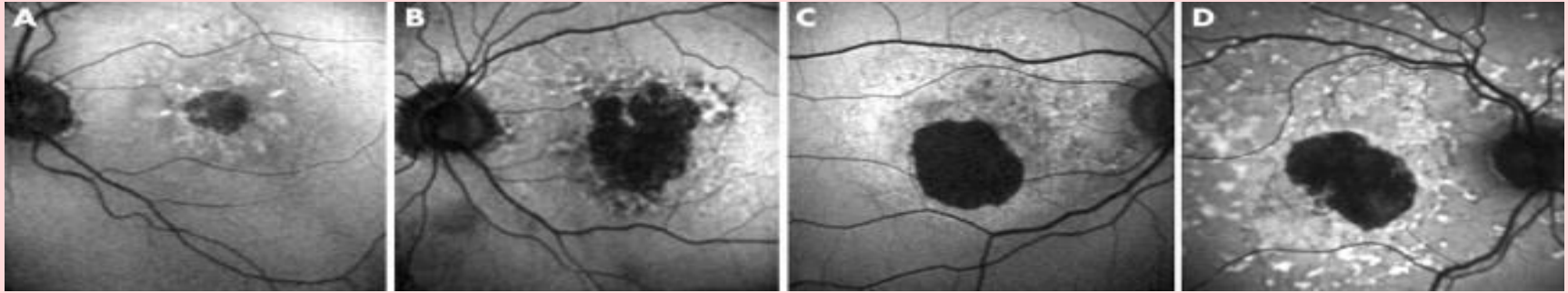
None



Focal



Banded

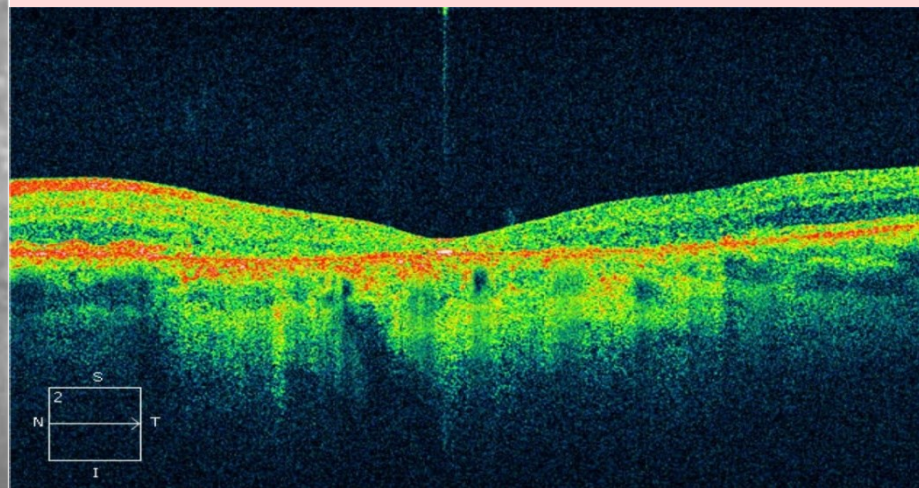
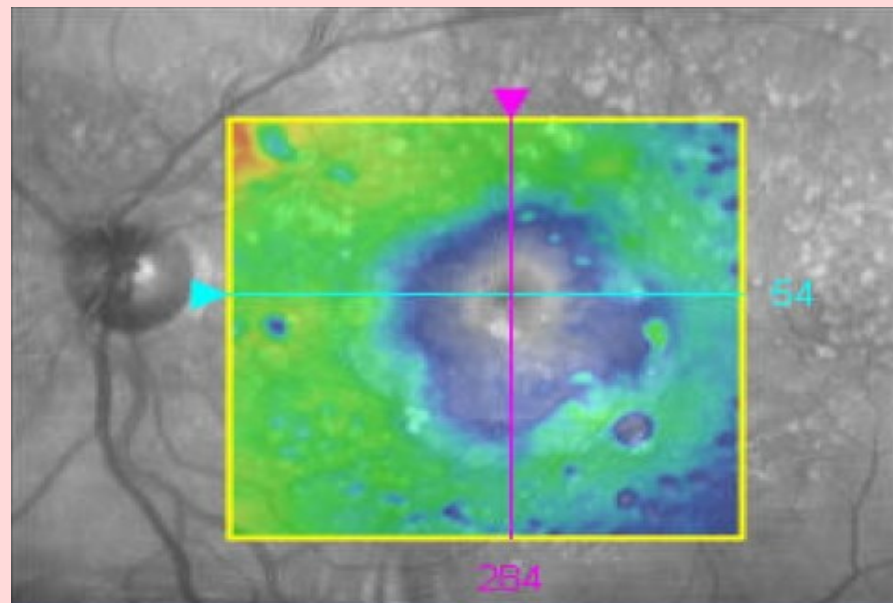


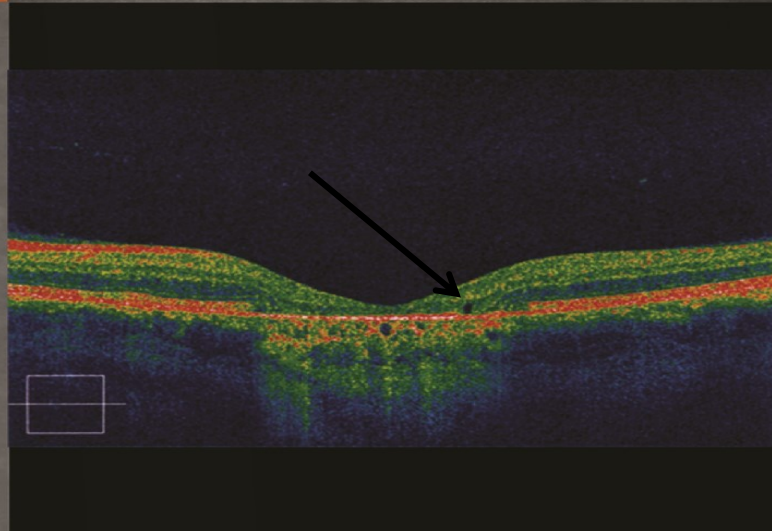
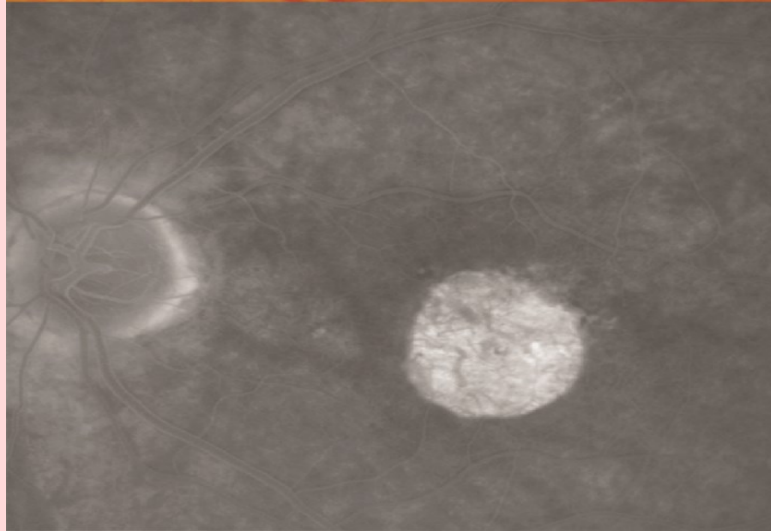
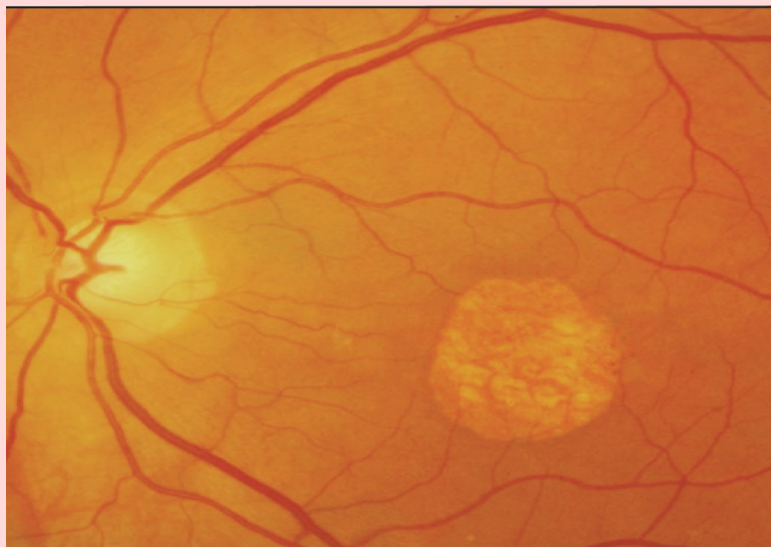
Diffuse

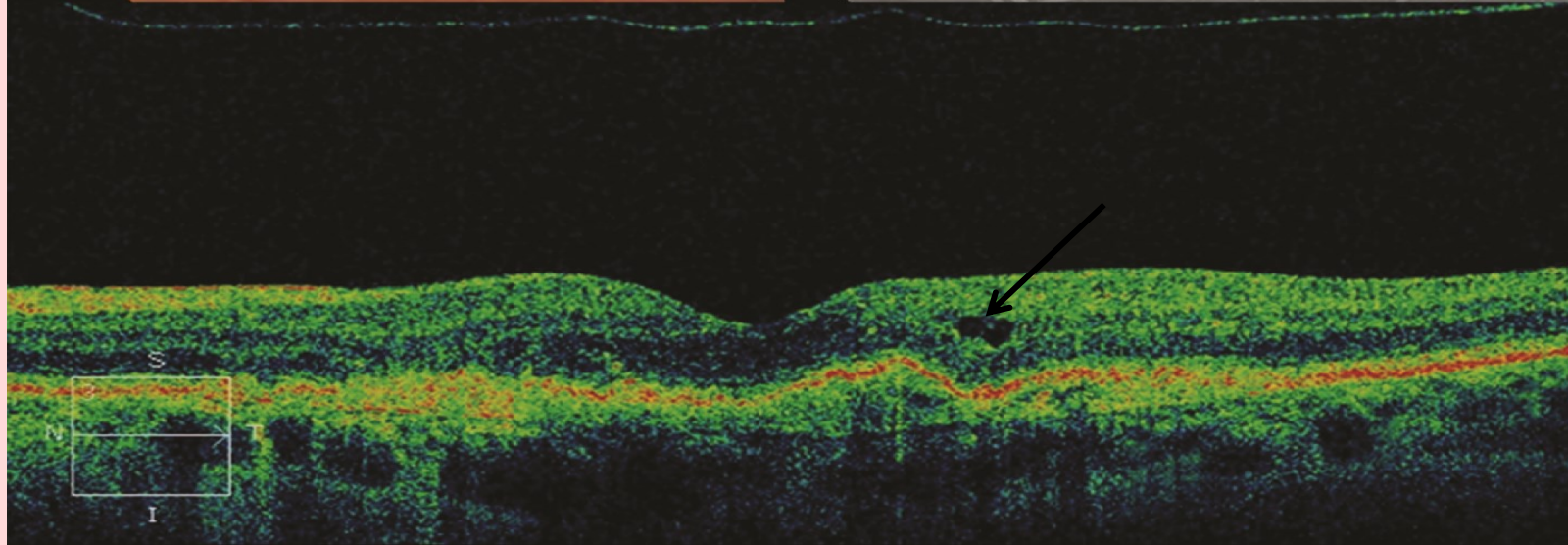
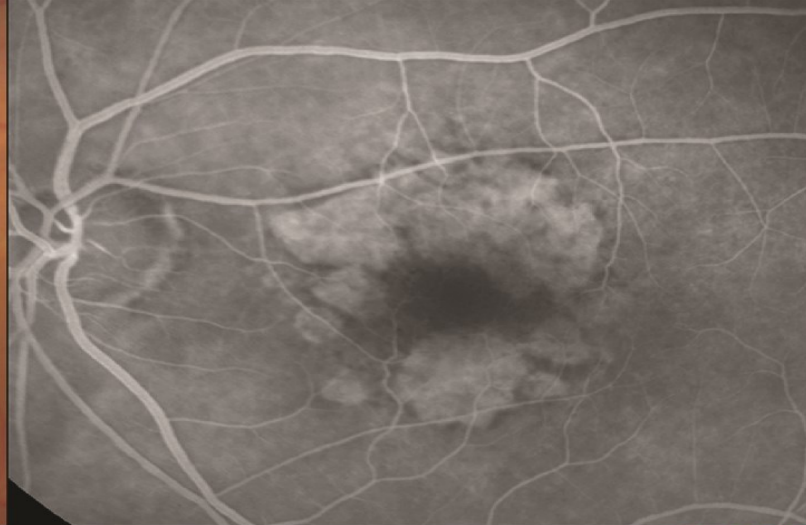
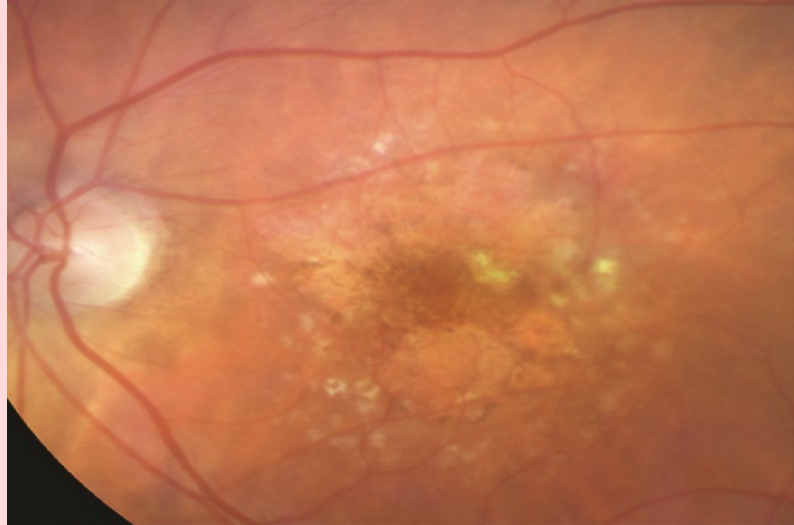
The area of increased FAF around the atrophy (difference between the CH and the total GA size at baseline) showed a positive correlation with GA enlargement over time ($\rho=0.60$; $P=0.0002$).

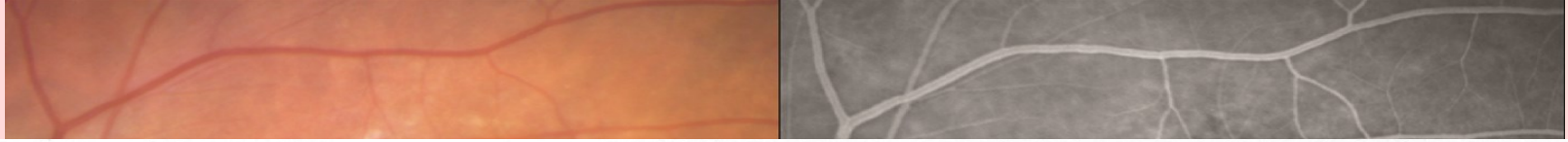
Schmitz-Valckenberg S et al. Correlation between the area of increased autofluorescence surrounding geographic atrophy and disease progression in patients with AMD.

Invest Ophthalmol Vis Sci. 2006 Jun;47(6):2648-5







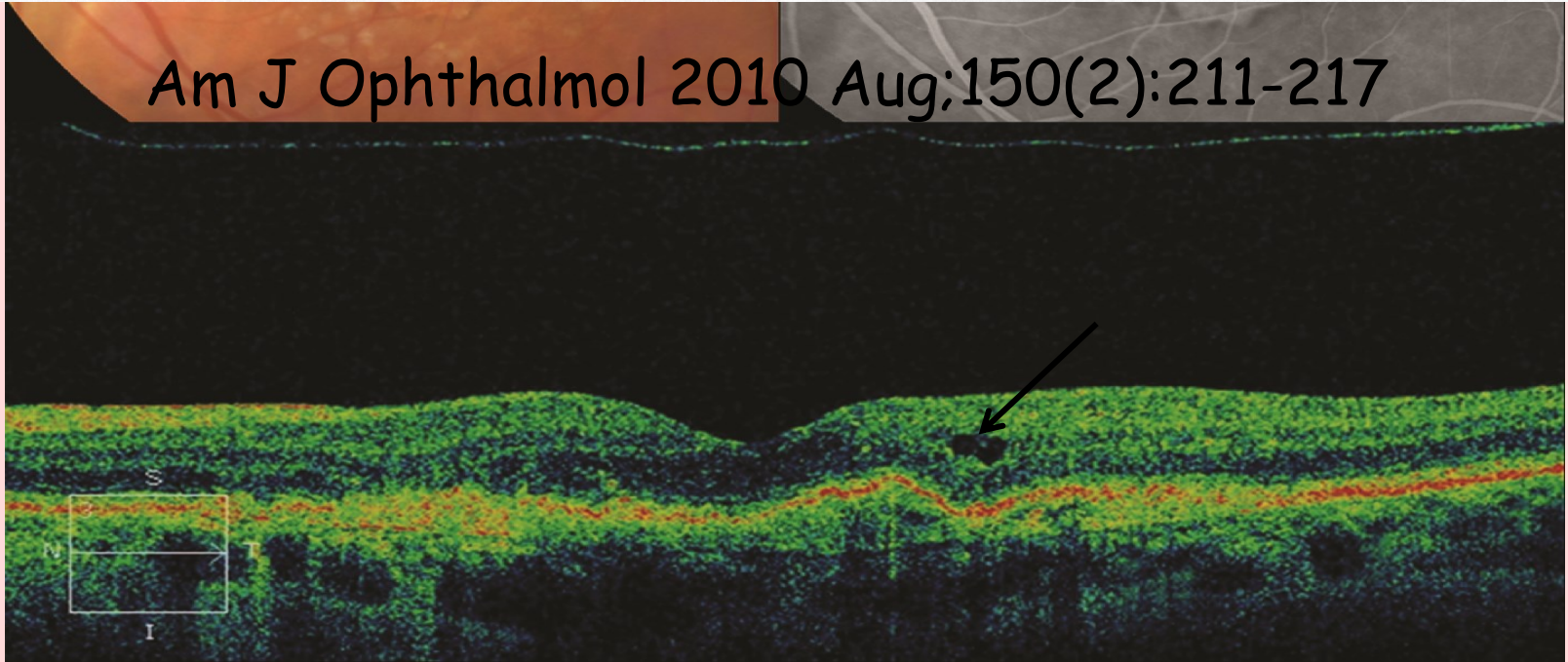


AQ: 1

Retinal Pseudocysts in Age-Related Geographic Atrophy

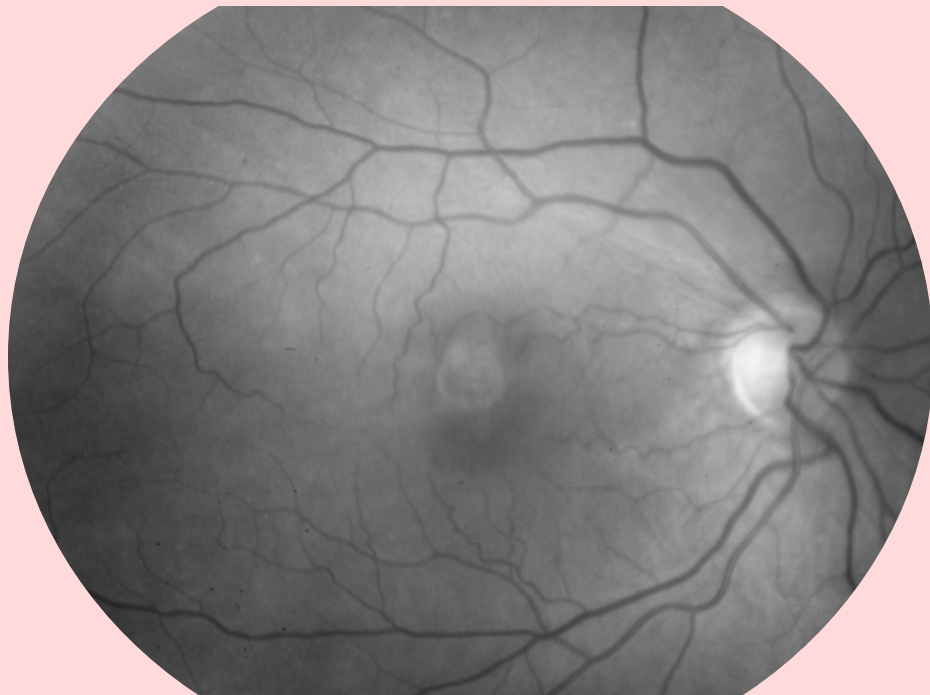
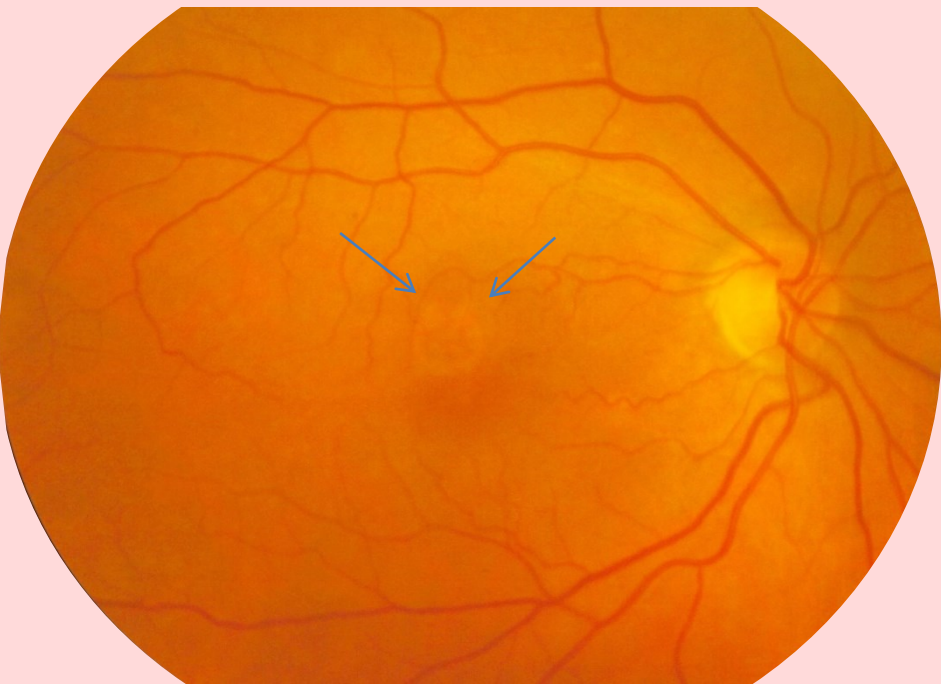
SALOMON Y. COHEN, LISE DUBOIS, SYLVIA NGHIEM-BUFFET, SANDRINE AYRAULT,
FRANCK FAJNKUCHEN, BRIGITTE GUIBERTEAU, CORINNE DELAHAYE-MAZZA, GABRIEL QUENTEL, AND
RAMIN TADAYONI

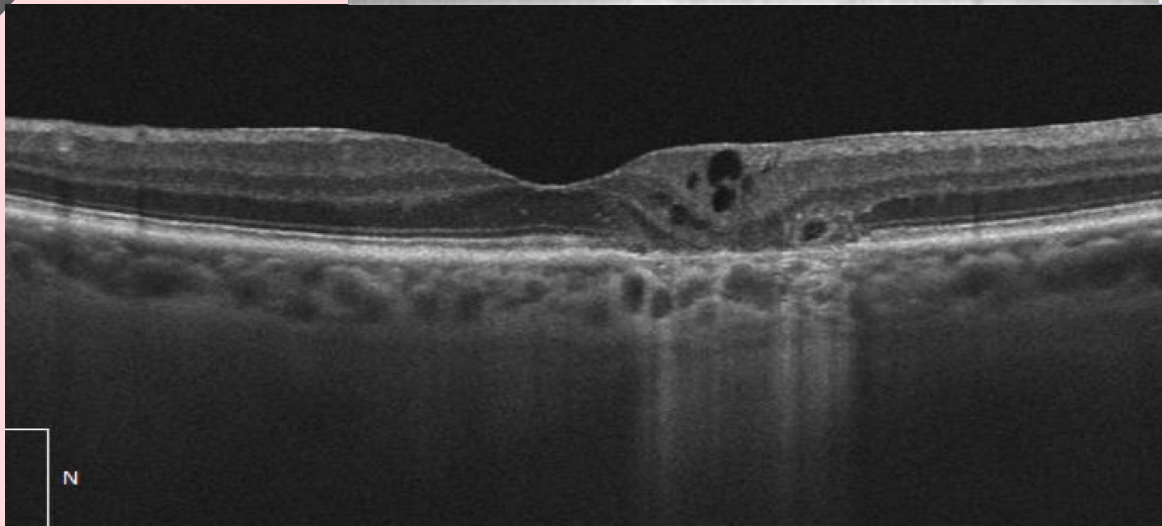
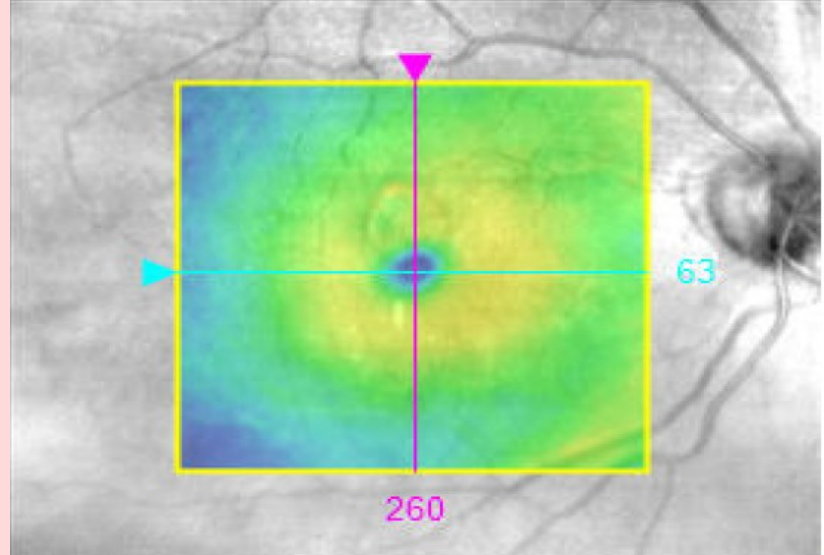
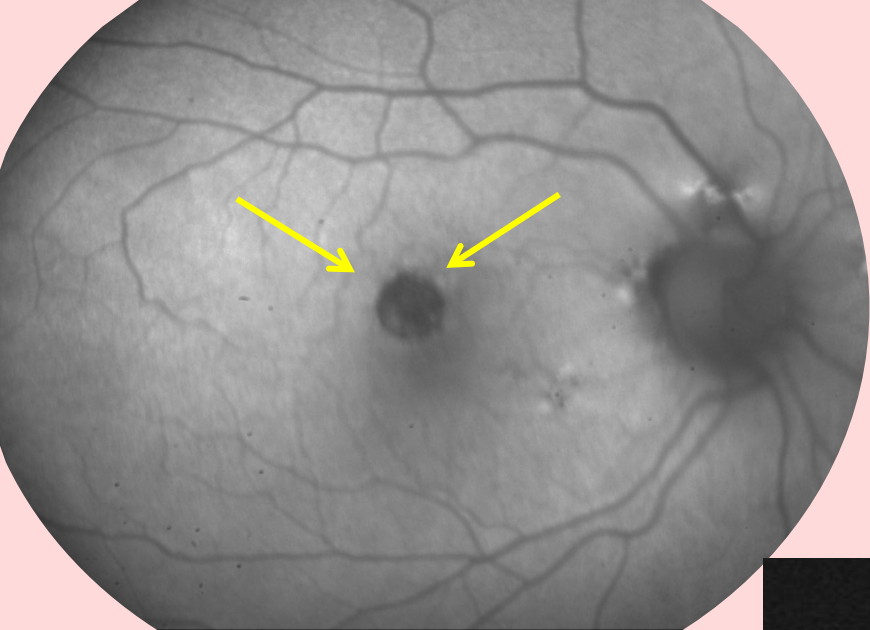
Am J Ophthalmol 2010 Aug;150(2):211-217



AJO 2010;150:211-217

- Eighty-eight eyes of 68 GA patients aged between 61 and 94 years (mean: 79.8) were examined.
- Twenty-four eyes (27.2%) exhibited pseudocysts corresponding to small cystoid spaces frequently located in the inner nuclear layer of the retina.
- There was no macular edema. Fluorescein angiography, performed in 71 eyes (80%), ruled out possible choroidal neovascularization.
- Their presence should not be considered as a manifestation of neovascular AMD





Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT Classification of Atrophy Report 3

Srinivas R. Sadda, MD,¹ Robyn Guymer, MBBS, PhD,² Frank G. Holz, MD,³ Steffen Schmitz-Valckenberg, MD,³ Christine A. Curcio, PhD,⁴ Alan C. Bird, MD,⁵ Barbara A. Blodi, MD,⁶ Ferdinando Bottoni, MD, FEBO,⁷ Usha Chakravarthy, MD, PhD,⁸ Emily Y. Chew, MD,⁹ Karl Csaky, MD,¹⁰ Ronald P. Danis, MD,⁶ Monika Fleckenstein, MD,³ K. Bailey Freund, MD,¹¹ Juan Grunwald, MD,¹² Carel B. Hoyng, MD, PhD,¹³ Glenn J. Jaffe, MD,¹⁴ Sandra Liakopoulos, MD,¹⁵ Jordi M. Monés, MD, PhD,¹⁶ Daniel Pauleikhoff, MD,¹⁷ Philip J. Rosenfeld, MD, PhD,¹⁸ David Sarraf, MD,¹⁹ Richard F. Spaide, MD,¹⁰ Ramin Tadayoni, MD, PhD,²⁰ Adnan Tufail, MD, FRCOphth,^{5,21} Sebastian Wolf, MD, PhD,²² Giovanni Staurenghi, MD, FARVO⁷
Ophthalmology. 2018 Apr;125(4):537-548

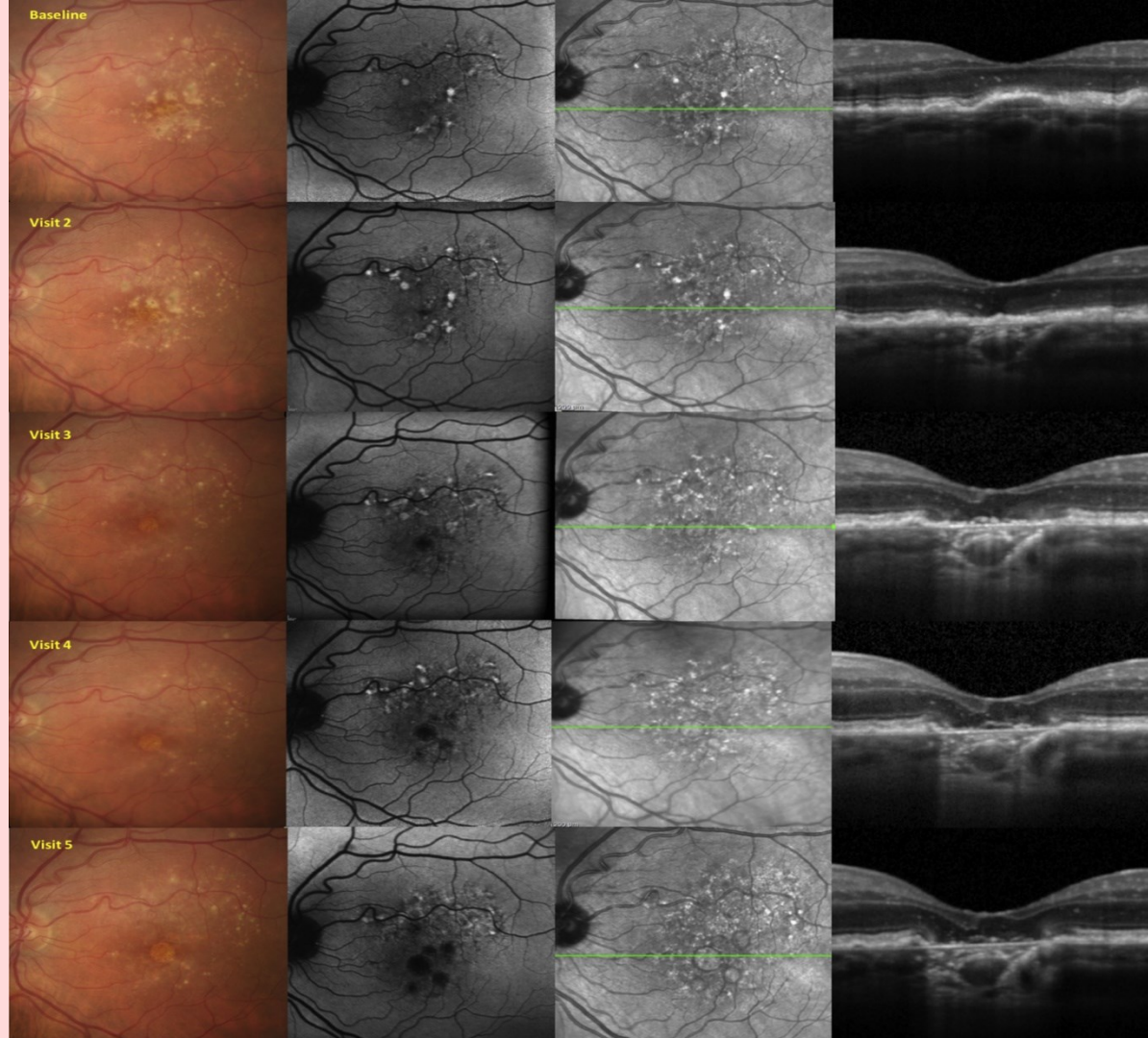
4 terms and histologic candidates were proposed: complete RPE and outer retinal atrophy (cRORA), incomplete RPE and outer retinal atrophy, complete outer retinal atrophy, and incomplete outer retinal atrophy.

Incomplete Retinal Pigment Epithelial and Outer Retinal Atrophy in Age-Related Macular Degeneration: Classification of Atrophy Meeting Report 4.

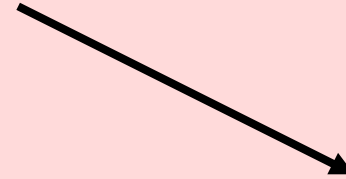
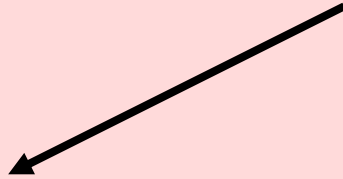
Guymer RH, Rosenfeld PJ, Curcio CA, Holz FG, Staurenghi G, Freund KB, Schmitz-Valckenberg S, Sparrow J, Spaide RF, Tufail A, Chakravarthy U, Jaffe GJ, Csaky K, Sarraf D, Monés JM, Tadayoni R, Grunwald J, Bottoni F, Liakopoulos S, Pauleikhoff D, Pagliarini S, Chew EY, Viola F, Fleckenstein M, Blodi BA, Lim TH, Chong V, Lutty J, Bird AC, Sadda SR.

Ophthalmology. 2020 Mar;127(3):394-409.

iRORA is defined on OCT as (1) a region of signal hypertransmission into the choroid, (2) a corresponding zone of attenuation or disruption of the RPE, and (3) evidence of overlying photoreceptor degeneration.



Formes Atrophiques



Discours

- DMLA « sèche »
- Autosurveillance
- Contrôles du FO

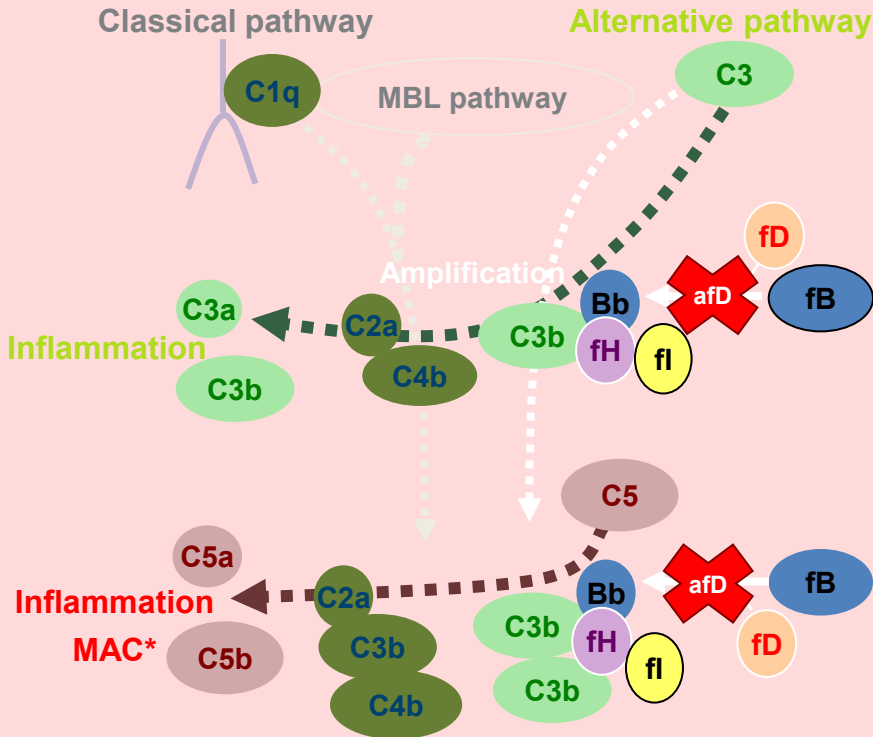
Prescription ?

- Antiox + Zinc
- Lutéine
- Zéaxanthine
- Éclairage ++
- Sur corrections
- Filtres ?

Stratégies pour prévenir la progression de la DMLA sèche

- Beaucoup d'espairs déçus
 - Prévenir l'accumulation de lipofuscin : Fenretinide
 - Prévenir la perte des photorecepteurs/EP: CNTF
 - Restauration cellulaire
 - Interagir avec la cascade du complément

Lampalizumab (anti-factor D): Selective Inhibitor of the Alternative Complement Pathway



Scientific Rationale

- Complement hyperactivity has been implicated in AMD
- Genetic polymorphisms in multiple alternative complement pathway loci are associated with the risk of AMD

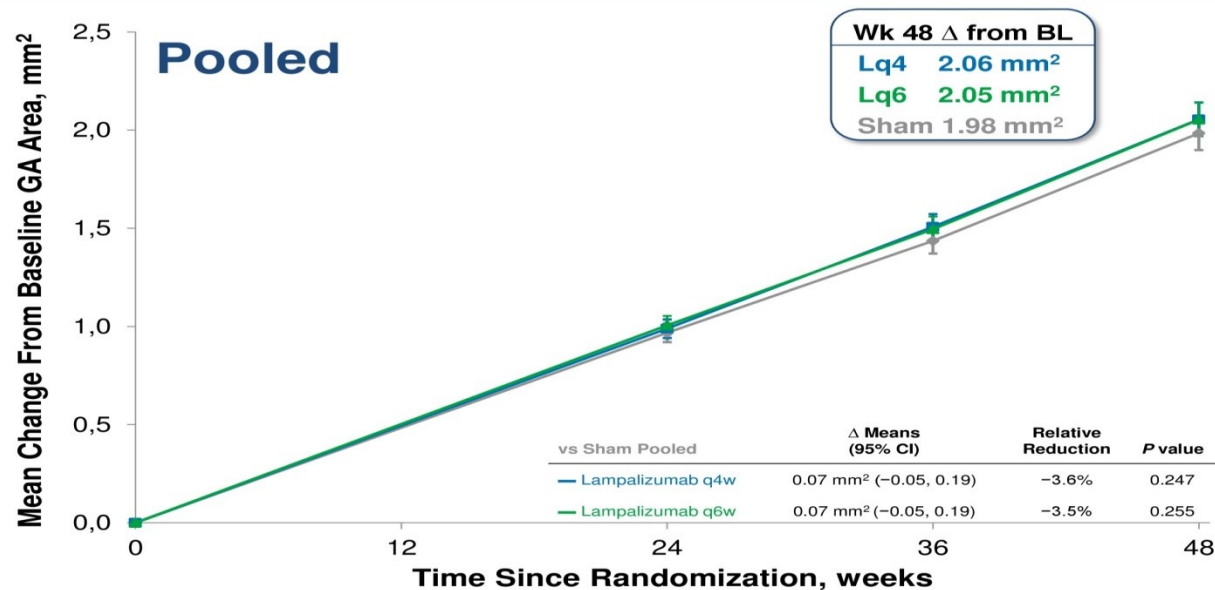
Complement factor D (fD)

- A rate-limiting enzyme in the alternative pathway

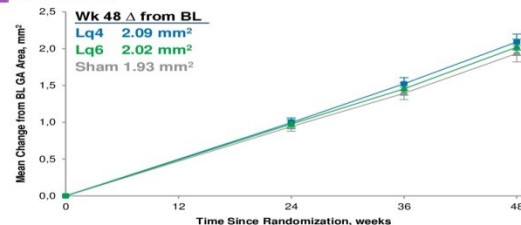
Lampalizumab (afD)

- Fab of a humanized monoclonal antibody
- Inhibits fD, blocking activation of the alternative complement pathway while preserving host-defense response

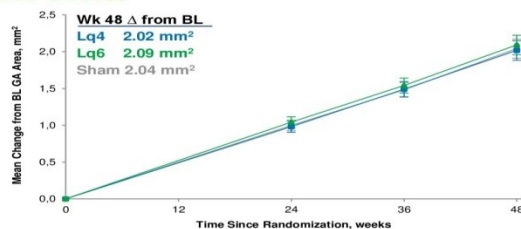
GA Area Growth From Baseline Over Time to Week 48



Spectri

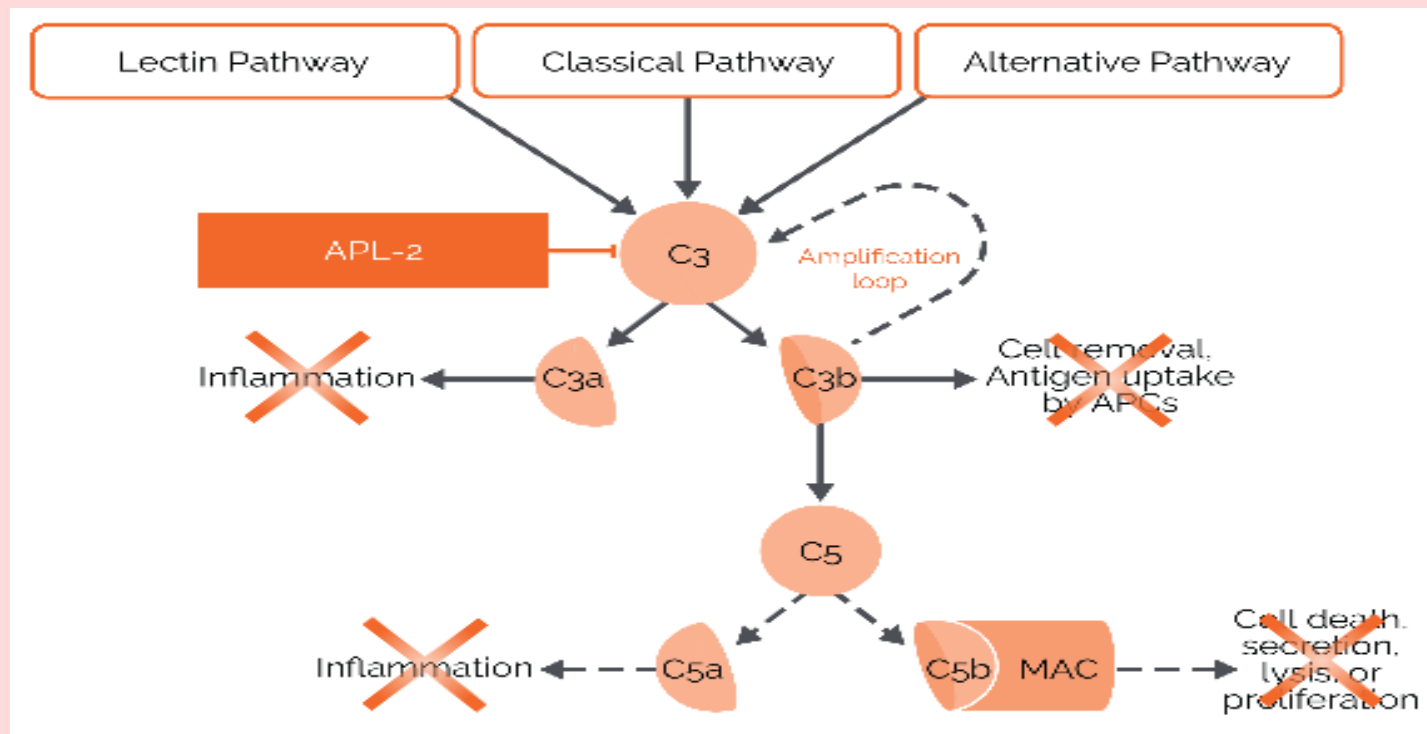


Chroma

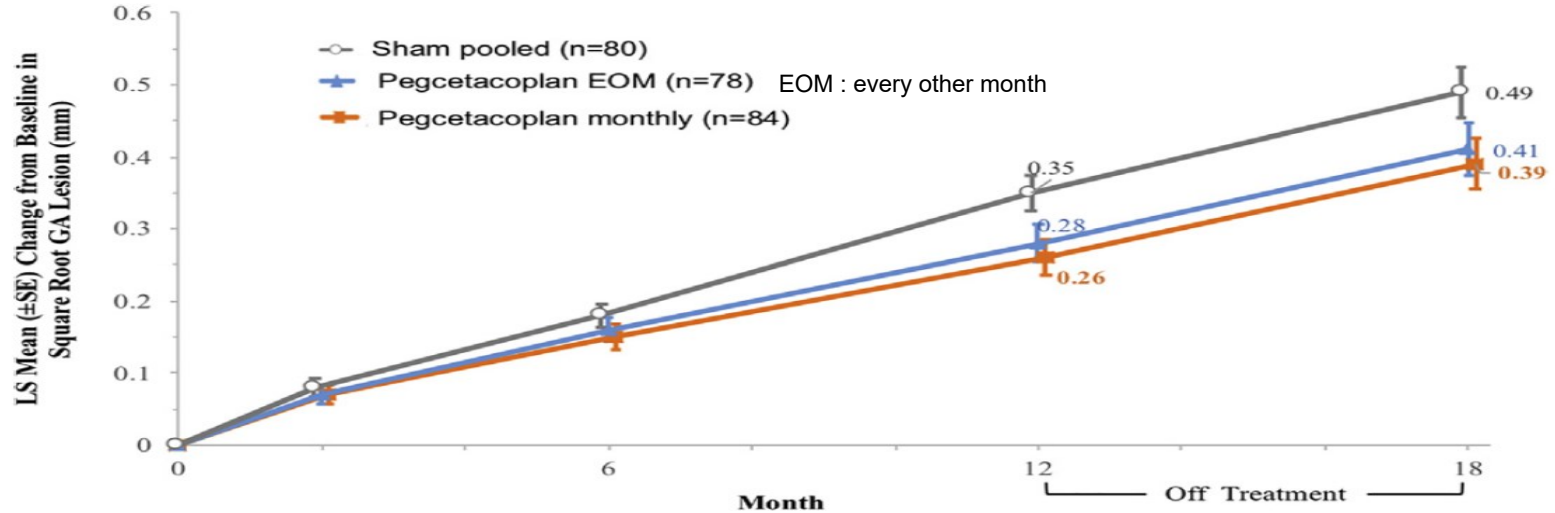


Mean change from baseline was estimated from a mixed-effect model repeated measures analysis adjusted for baseline GA area, subfoveal vs non-subfoveal location, and multifocal vs non-multifocal configuration; complement factor I (CFI)-profile biomarker status; baseline best-corrected visual acuity category; and sex. Pooled analysis included an additional covariate adjustment for study. Error bars are 95% CIs. GA, geographic atrophy; q4w, every 4 weeks; q6w, every 6 weeks. . ClinicalTrials.gov, Spectri: NCT02247531; Chroma: NCT02247479.

APL-2 : Anti-C3



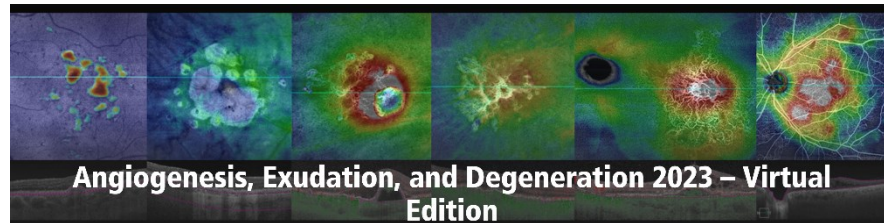
APL-2 : Anti-C3



APL-2 : Phase 3 Derby et Oaks

9 Septembre 2021

Pegcetacoplan vs. Injection simulée	mensuel	p	bimestriel	p
OAKS	diminution 22%	0,0003	diminution 16%	0,0052
DERBY	diminution 12%	0,0528	diminution 11%	0,075
OAKS + DERBY: extrafoveal	diminution 26%	<0,0001	diminution 23%	0,0002



Elodie Bousquet
Paris

Session IV: Pegcetacoplan Results for the Treatment of GA: Derby and Oaks Trials

2-year Outcomes of the Pegcetacoplan Phase 3 Derby and Oaks Clinical Trials for GA: Safety and Exudative Changes

Rishi Singh, MD

2-year Outcomes of the Pegcetacoplan Phase 3 Derby and Oaks Clinical Trials for GA: Safety and Exudative Changes

- **Inflammations intraoculaires** (3.8% dans le groupe IVT tous les mois) en partie liée à l'impureté du médicament en 2018.
- 80% des inflammations étaient minimales ou modérées. Les patients ont continué le traitement sans récurrence de l'inflammation.
- Pas de cas de vascularite occlusive.
- Endophtalmies: 0.034% par injection (taux superposable aux IVT d'anti-VEGF).

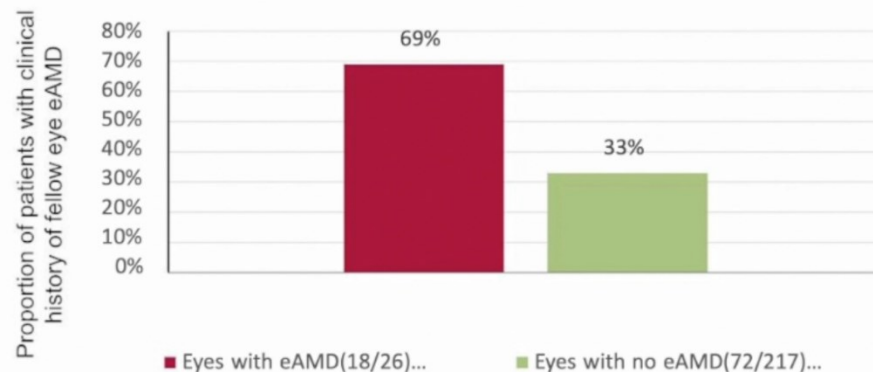
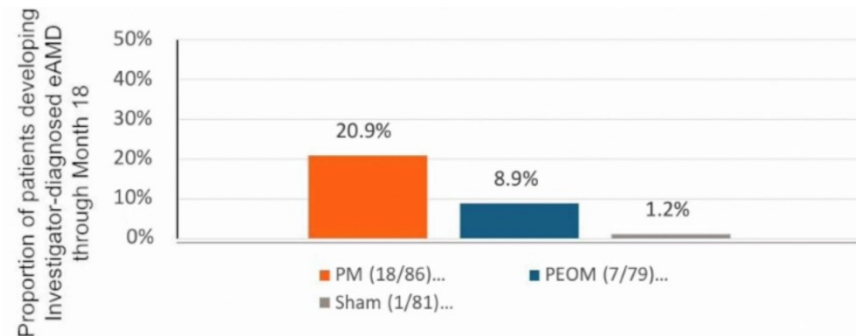
OAKS and DERBY combined

	PM (N=419)	PEOM (N=420)	Sham Pooled (N=417)
Intraocular inflammation			
12 months, n (%)	9 (2.1%)	4 (1.0%)	0
24 months - cumulative, n (%)	16 (3.8%)	9 (2.1%)	1 (0.2%)
Infectious endophthalmitis			
12 months, n (%)	1 (0.2%)	2 (0.5%)	0
24 months - cumulative, n (%)	2 (0.5%)	2 (0.5%)	0

2-year Outcomes of the Pegcetacoplan Phase 3 Derby and Oaks Clinical Trials for GA: Safety and Exudative Changes

Effet secondaire principal mis en évidence par l'étude FILLY de phase 2: **conversion en DMLA exsudative** :

- 21% des patients en IVT/mois; 9% des patients en IVT / 2 mois; 1% des patients groupe placebo.
- La survenue de néovaisseaux choroïdiens est plus fréquente chez les patients avec une DMLA exsudative dans l'œil controlatéral (69% des cas).
- Les patients avec **DLS (double layer sign)** qui témoigne d'un néovaisseau de type 1 sous jacent n'était pas exclu et représentaient 37% des patients inclus.



2-year Outcomes of the Pegcetacoplan Phase 3 Derby and Oaks Clinical Trials for GA: Safety and Exudative Changes

- Dans les études de phase 3 Derby et Oak: possibilité de traiter par anti-VEGF en plus des IVT de pegcetacoplan en cas de conversion en DMLA exsudative.
- A 2 ans: **12%** des patients en IVT/mois; **7%** des patients en IVT / 2 mois; **3%** des patients groupe placebo ont développé des néovaisseaux.
- La plupart des néovaisseaux étaient de type 1 (sous l'épithélium pigmentaire).
- Tous les patients avec néovaisseaux ont bénéficié d'un traitement combiné : anti-VEGF et IVT de pegcetacoplan

OAKS and DERBY combined

	PM (N=419)	PEOM (N=420) ^b	Sham Pooled (N=417)
New-onset investigator-determined eAMD 12M, n (%)	25 (6.0%)	17 (4.1%)	10 (2.4%)
New-onset investigator-determined eAMD, 24M - cumulative, n (%)	51 (12.2%)	28 (6.7%)	13 (3.1%)
Confirmed by reading center, 24M, N (%) At time of investigator-reported eAMD, 100% of patients had available SD-OCT and 82% had available FA for reading center evaluation	37 (8.8%)	23 (5.5%)	11 (2.6%)

Conclusion

- Pegcetacoplan (injection mensuelle ou bimensuelle) ralentit la progression de l'atrophie avec **une efficacité qui semble augmenter avec la durée du traitement.**
- Effets secondaires évalués sur 1200 patients (12 000 injections) à 2 ans:
 - Principale complication: **néovaisseaux choroïdiens** :
 - 12.2% des patients injectés tous les mois
 - 6.7% des patients injectés tous les deux mois
 - 3.1% des groupes témoins.
 - Autres effets secondaires liés aux injections intravitréennes comparables aux IVT d'anti-VEGF.



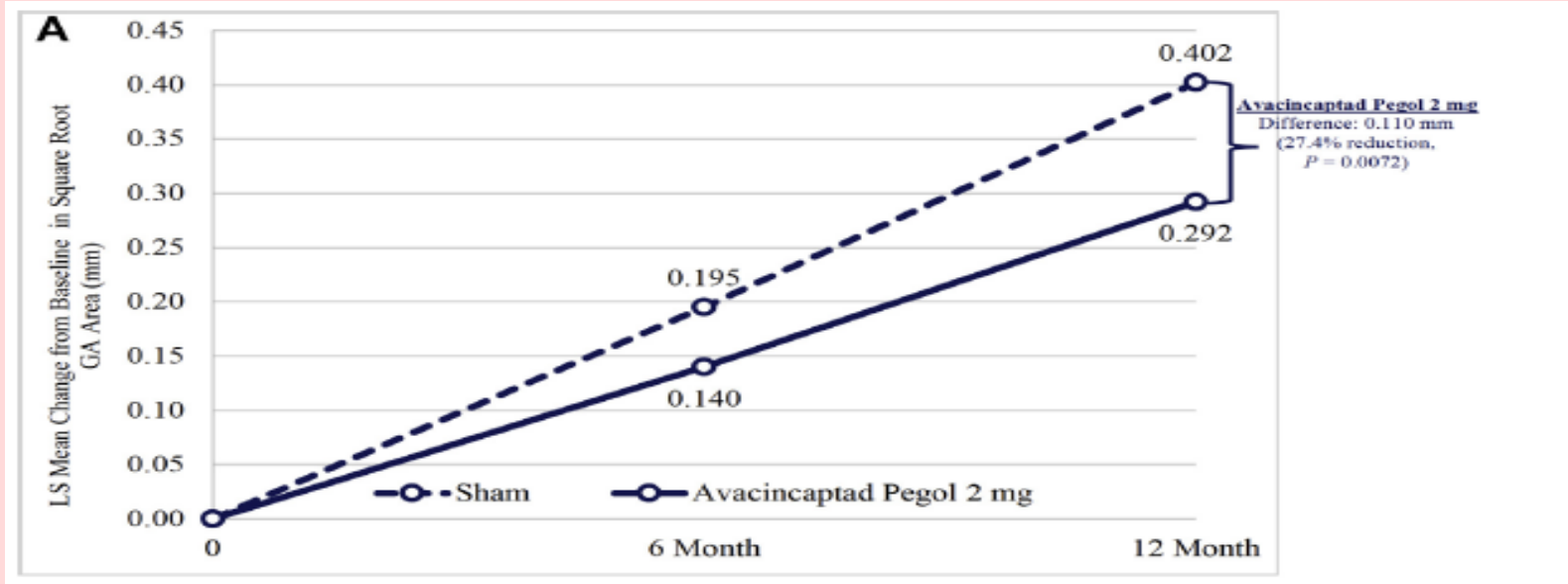
Agreement FDA

SYFOVRE is approved for GA patients with or without subfoveal involvement and provides dosing flexibility for patients and physicians with a dosing regimen of every 25 to 60 days. In the OAKS and DERBY studies, SYFOVRE reduced the rate of GA lesion growth compared to sham and demonstrated increasing treatment effects over time, with the greatest benefit (up to 36% reduction in lesion growth with monthly treatment in DERBY) occurring between months 18-24

The cost for Syfovre intravitreal solution (150 mg/mL) is around \$2,316 for a supply of 0.1 milliliters, depending on the pharmacy you visit.

Anti C-5

Zimura[®] (avacincaptad pegol)



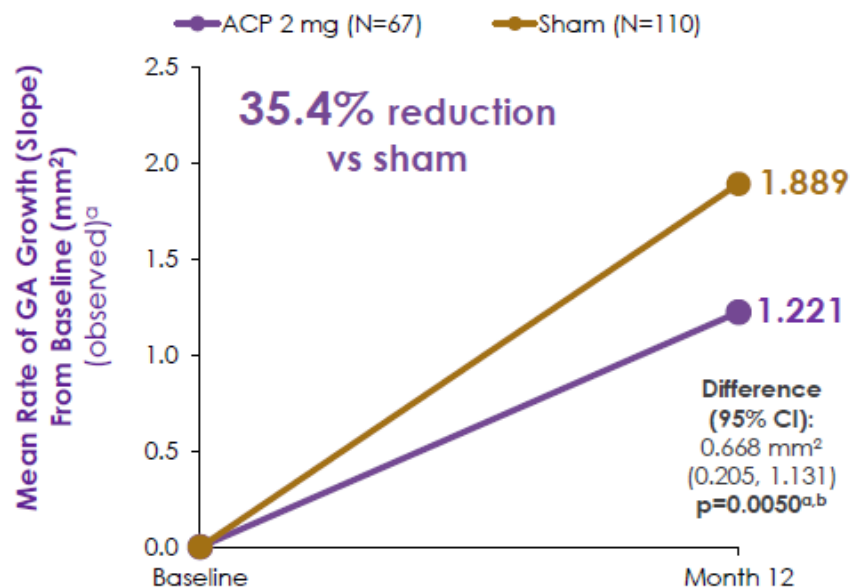
Anti C-5

Zimura[®] (avacincaptad pegol), a novel complement C5 inhibitor, for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

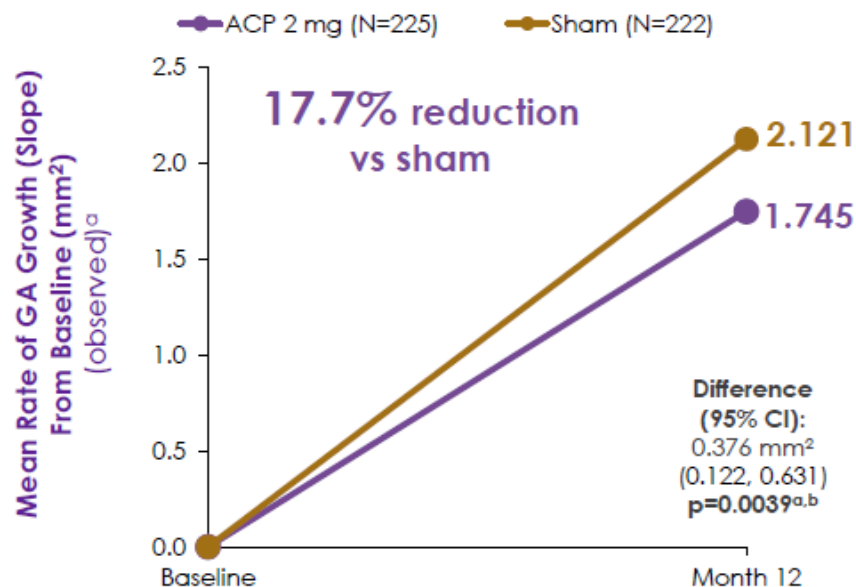
The reduction in the mean rate of GA growth over 18 months was 28.11% for the Zimura 2 mg group as compared to the corresponding sham control group and 29.97% for the Zimura 4 mg group as compared to the corresponding sham control group.

Mean rate of observed GA growth (slope analysis) demonstrated consistent efficacy results between the two studies

GATHER1



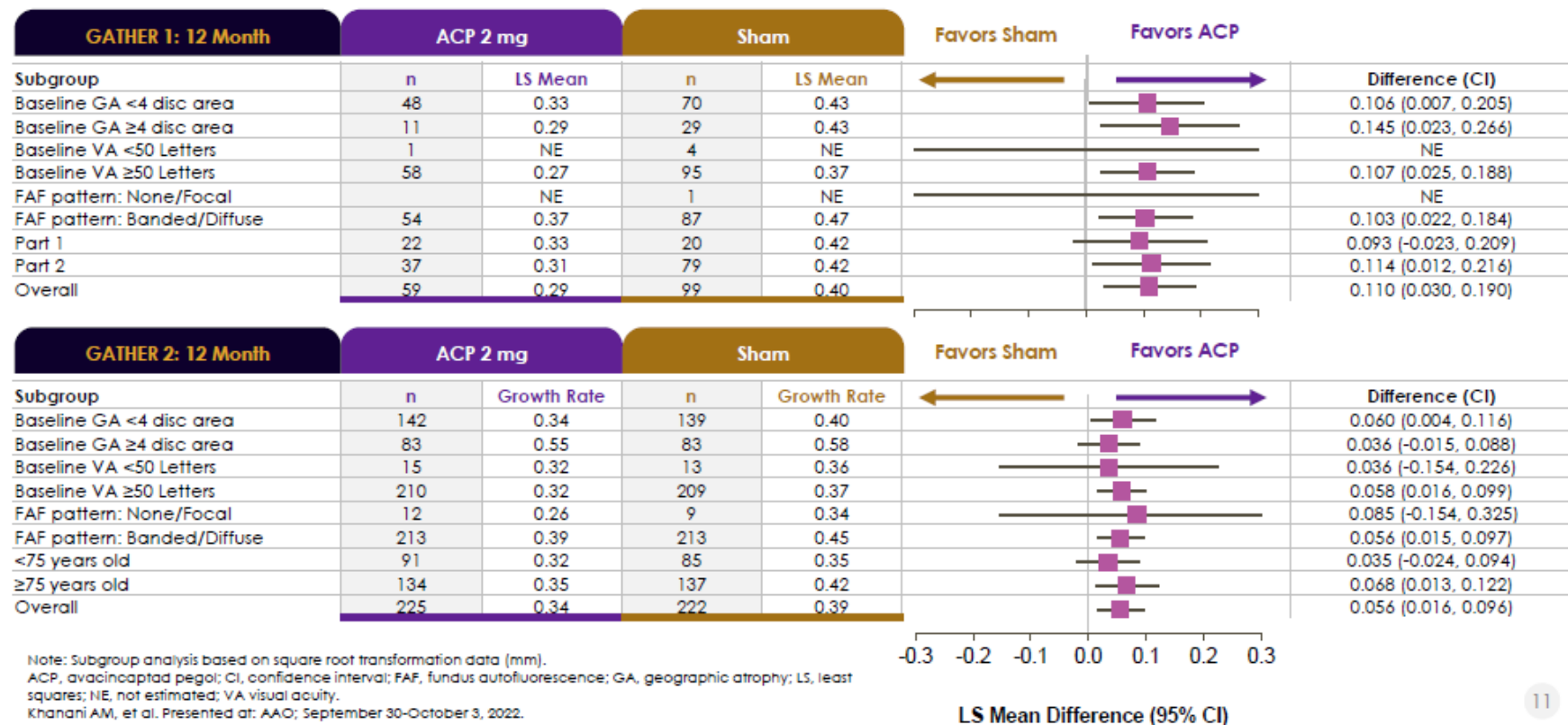
GATHER2



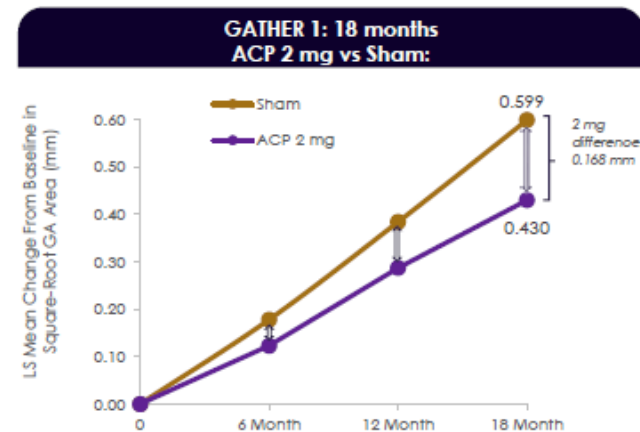
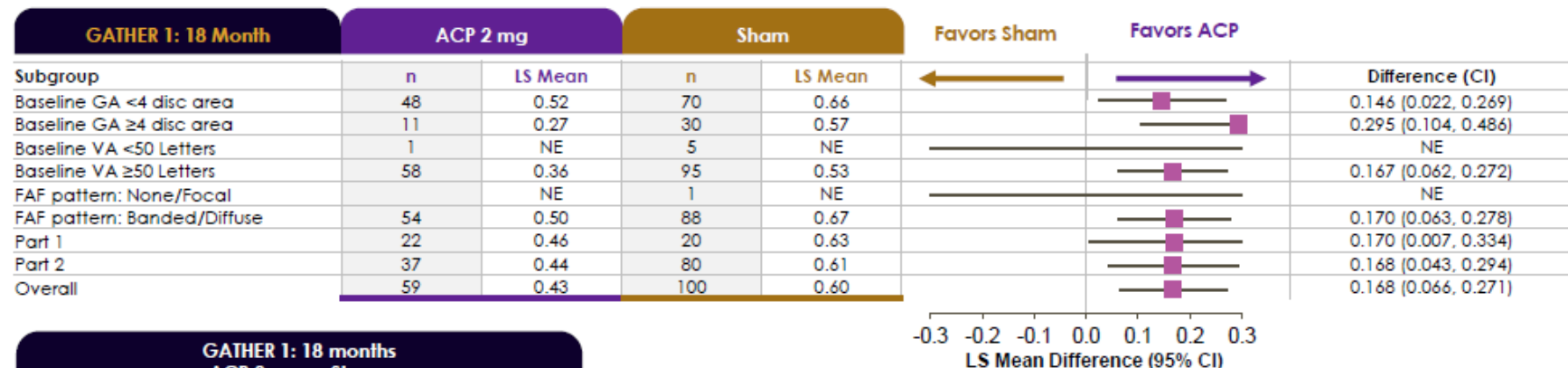
Note: The primary analysis for GATHER1 (mean change in square root transformed GA area from baseline to month 12 [mm]) is consistent with the slope analysis utilizing observed data. The estimates for the GATHER1 ACP 2 mg group vs sham are from the MMRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2 of the trial, and should not be interpreted as directly observed data. ^aNon-square root transformation; ^bDescriptive p-value.

ACP, avacincaptad pegol; CI, confidence interval; GA, geographic atrophy.
Data on file. IVERIC bio.

Benefit across subgroups is consistent among the pivotal GATHER1 and GATHER2 studies



Benefit across subgroups seen in GATHER1 increases with duration of therapy over 18 months



Note: Subgroup analysis based on square root transformation data (mm).

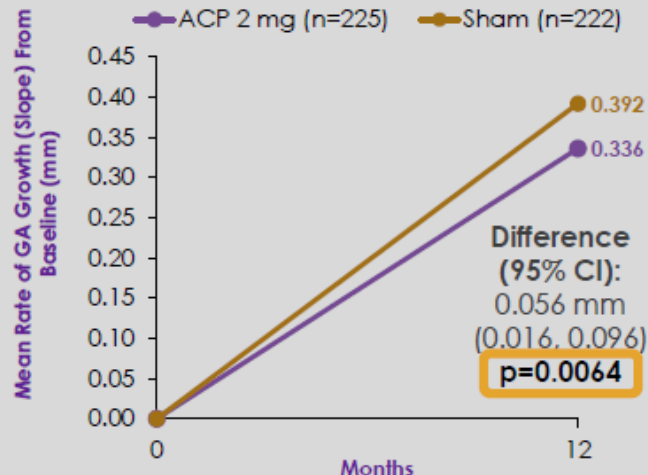
ACP, avacincaptad pegol; CI, confidence interval; FAF, fundus autofluorescence; GA, geographic atrophy; LS, least squares;

NE, not estimated; VA, visual acuity.

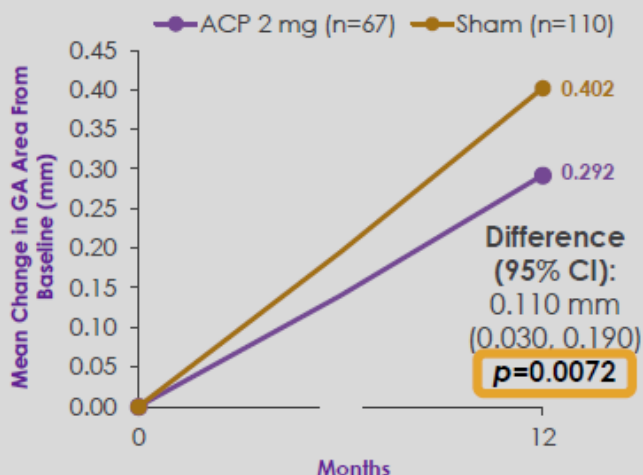
Khanani AM, et al. Presented at: AAO; September 30-October 3, 2022.

Avancincaptad pegol is the first investigational therapy in GA to achieve the 12-month prespecified, primary endpoint, in two pivotal, phase 3 studies

GATHER 2



GATHER 1



Perspectives thérapeutiques

Echec de Spectri et Chroma

APL-2 : résultats en demi-teinte mais agreement FDA

Zimura : résultats meilleurs, en attente d'agreement

Beaucoup d'espoirs à long terme

S'habituer à l'analyse des clichés en autofluorescence

Prudence dans le discours et les délais d'obtention de thérapeutiques efficaces

En attendant une thérapie

Améliorer les contrastes: éclairage, tablettes numériques
Systèmes optiques et électroniques
Bilan orthoptique et rééducation orthoptique des basses
visions +++
