Science For A Better Life

Dry AMD – Industry View

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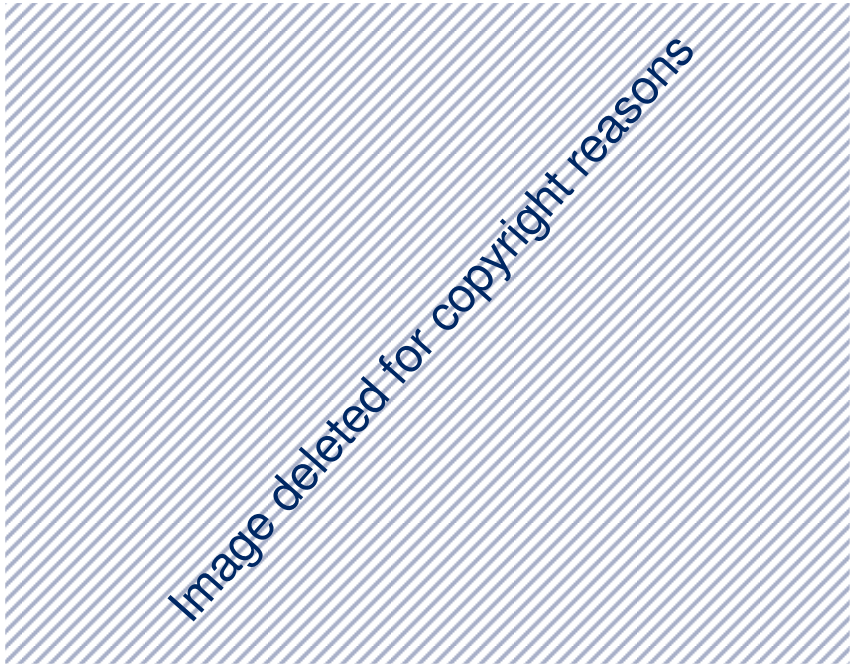
Disclaimer: The presentation reflects the personal opinion of the presenter and not necessarily the opinion of his employer or the „industry“ in general.

Overview

- Proposed Endpoints and Indicators of Efficacy
  - Drusen Area
  - Drusen Volume
  - Drusen Evaluation
  - Geographic Atrophy Area
  - Increased Autofluorescence in Junctional Zone
- General Trial Design Considerations
  - Comparator
  - Trial Duration

Endpoints in Dry AMD

- Visual acuity deteriorates very slowly in Dry AMD
  - Timeframe exceeds the duration of development programs
- Visual acuity reflects only a subset of vision changes in Dry AMD
  - More sophisticated changes are difficult to capture

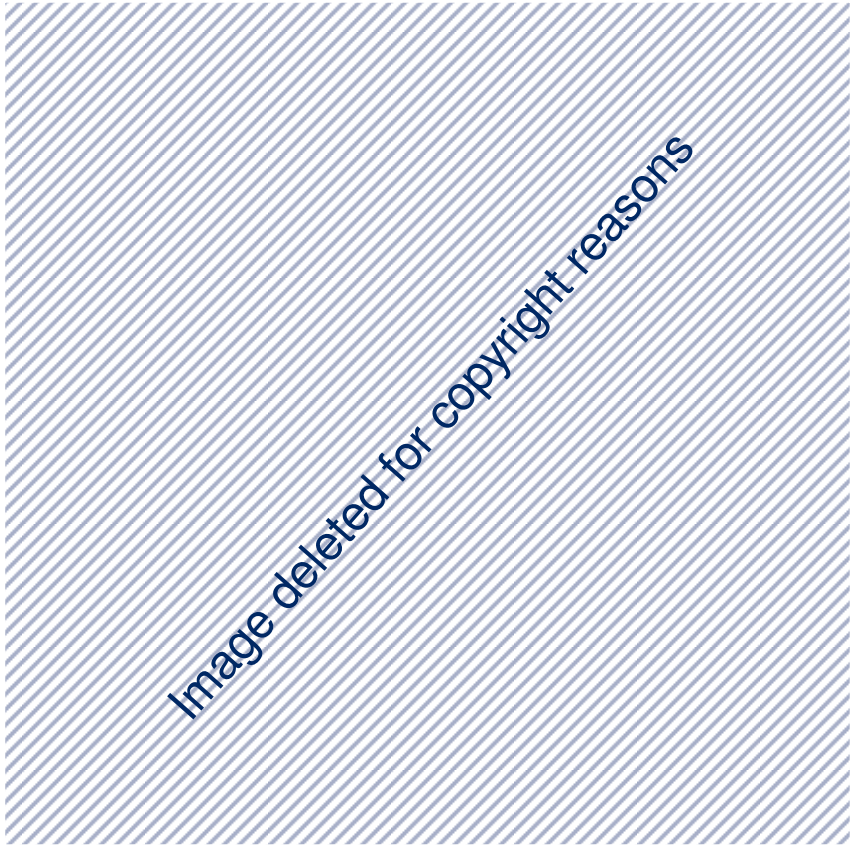


The AREDS results show the slow course of onset of vision loss in dry AMD patients as well as the mild treatment effects of the AREDS medication.

Source and image: AREDS report No. 8; Arch Ophthalmol (2001) 119:1417-36

Endpoints: Drusen Area

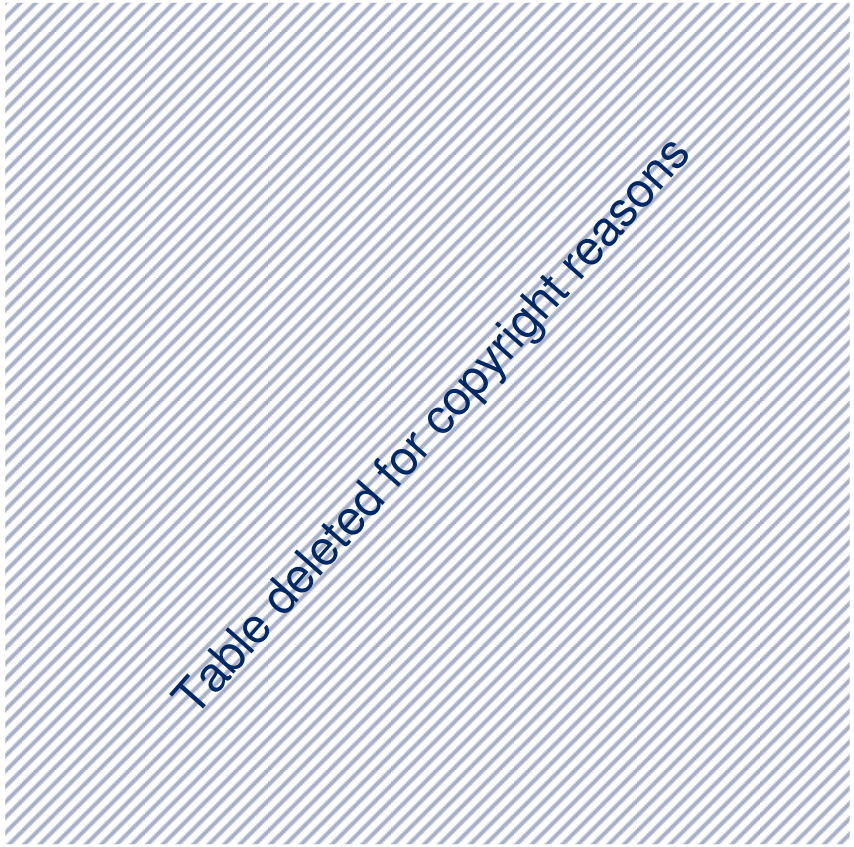
Drusen area and volume can be quantified by advances fundus imaging technologies using overlay techniques of SD-OCT and fundus-fotography.



Source and image: Yehoshua Z. et al. (2011) Semin Ophthalmol 26:167-80

Endpoints: Drusen Area and Volume

The table shows the proportion of patients having decreased/stable/increased Drusen area and volume at 6/12/18/24 months of follow-up. 13-17% show at all time points spontaneous regression, while 22-69% show progression over time in either Drusen area or volume.



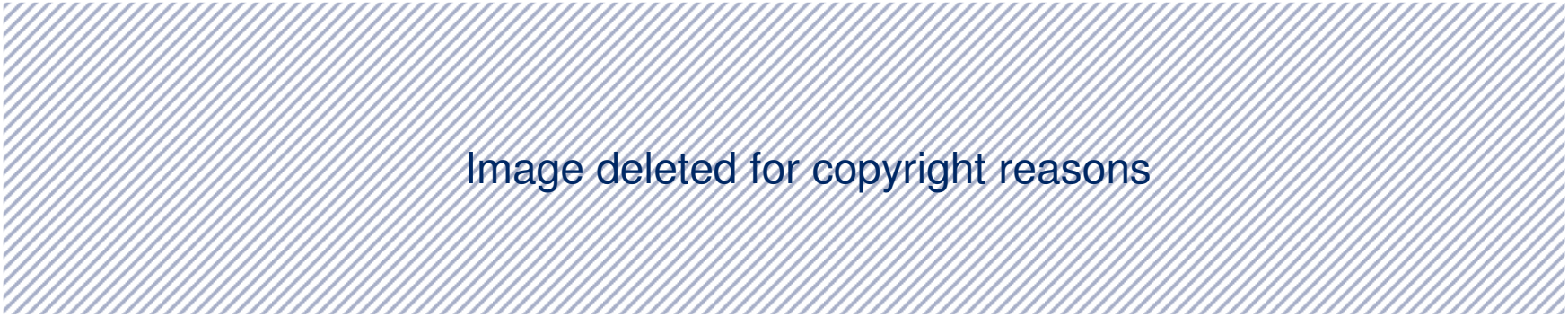
Source and table: Yehoshua Z. et al. (2011) Ophthalmology epub Jul 1

Endpoints: Drusen Volume and Area

- Percentage of patients with decreased, stable and increased area or volume might considered as a indicator of efficacy
- Further characterization of this parameter is required as disappearance of Drusen might also indicate GA development/progression.
- Focus on subpopulation with particularly high risk of increase in drusen volume or area might reduce sample size

Source: Landa G. et al. (2011) J Ocul Pharmacol Ther 27:77-82

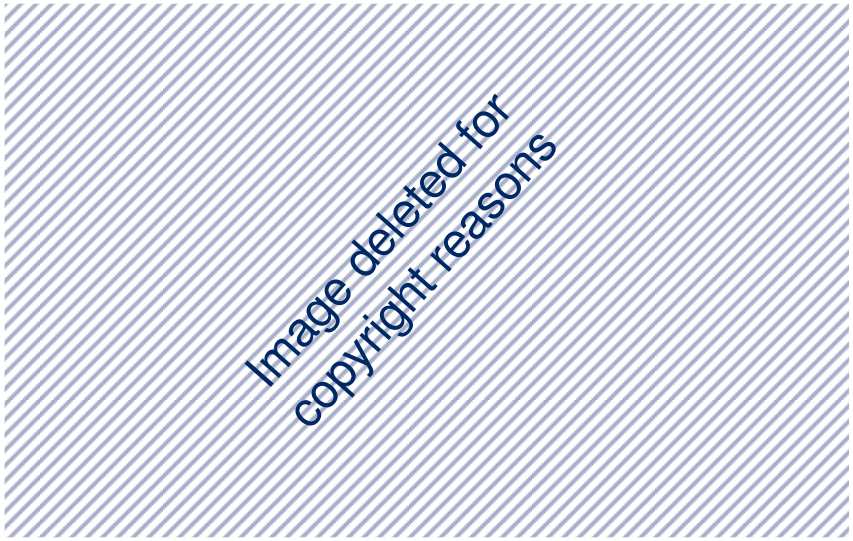
Endpoints: Evaluation of Drusen



- Shape (convex / concave)
- Internal reflectivity (low / medium / high)
- Homogeneity (homogenous / non-homogenous)
- Presence of central core
- Presence of overlying foci of hyperreflectivity

Source and image: Landa G. et al. (2011) J Ocul Pharmacol Ther 27:77-82

Endpoints: Evaluation of Drusen



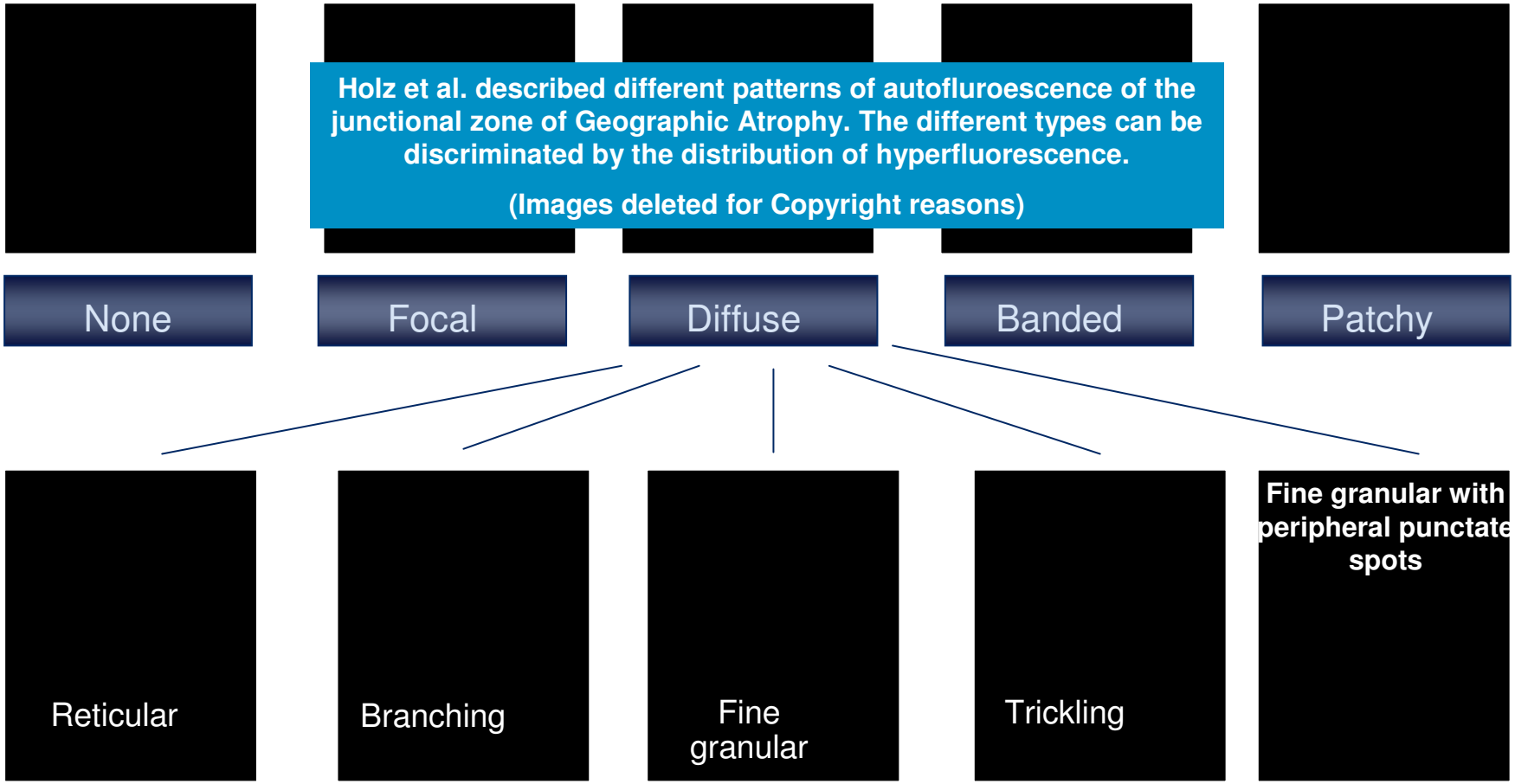
Drusen dissolved after therapy*

Drusen regressed after therapy*

(Images show typical examples pre-/post treatment)

*Experimental treatment with glatiramer acetate weekly within a pilot study
Source and image: Landa G. et al. (2011) J Ocul Pharmacol Ther 27:77-82

Endpoints: Autofluorescence Patterns



A Bindewald et al. FAM Study Group ***Br J Ophthalmol*** 89:874-878, 2005

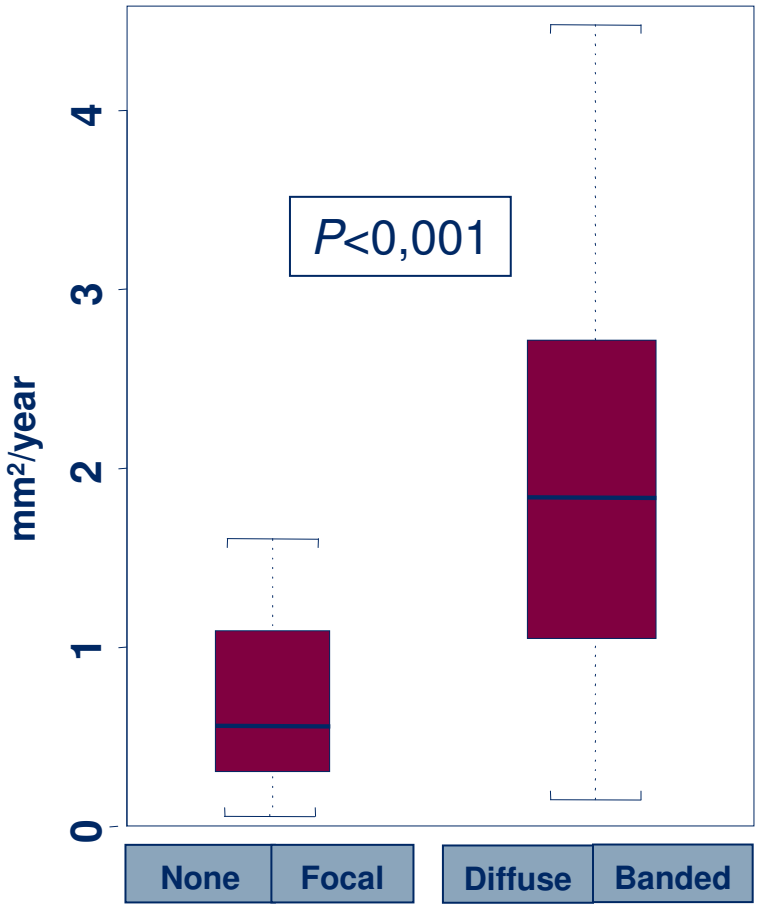
Endpoints: Geographic Atrophy Area

None/Focal autofluorescence pattern in junctional zone

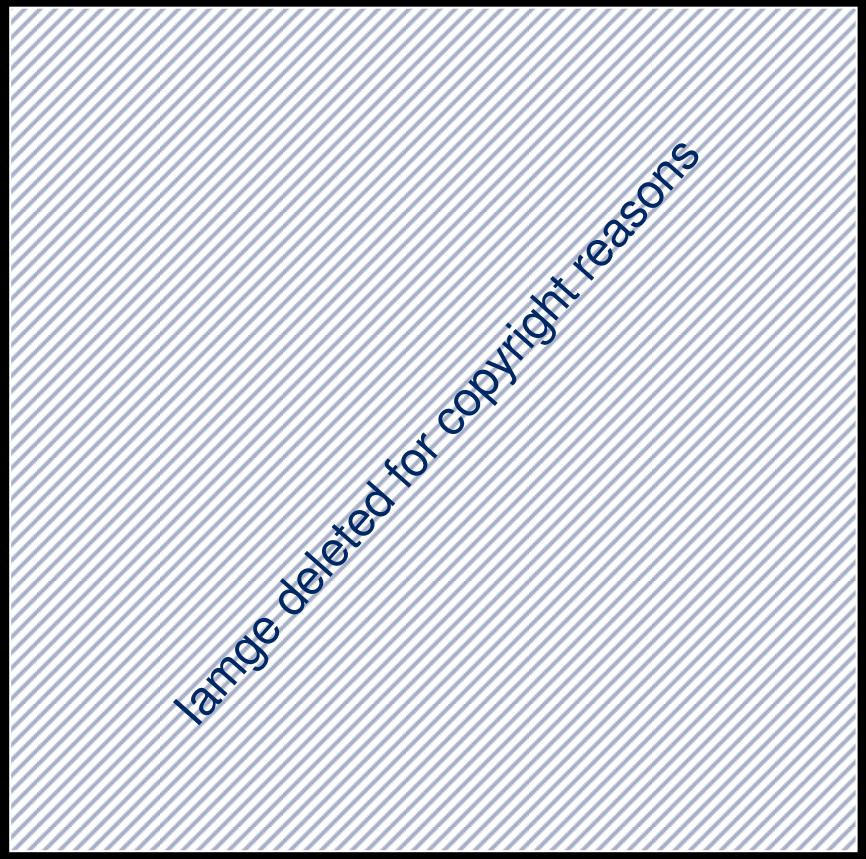
0.51 mm^2/year (median)

Diffuse/banded autofluorescence pattern in junctional zone

1.77 mm^2/year (median)



Holz et al. FAM-Study Group. ***Am J Ophthalmol 143:463-72, 2007***
Figure: Courtesy of Frank Holz



Geographic Atrophy Area increases over time and can be assessed

- semiquantitatively
- longitudinally
- highly reproducible

Proposal for endpoints: Comparison of GA area at two timepoints.

Source and image: Schmitz-Valckenberg S et al. (2011) Inv Ophthalmol Vis Sci 52:7640-6

Endpoints: Increased Autofluorescence Signal in Junctional Zone

None/Focal autofluorescence pattern in junctional zone

0.51 mm^2/year (median)

Diffuse/banded autofluorescence pattern in junctional zone

1.77 mm^2/year (median)

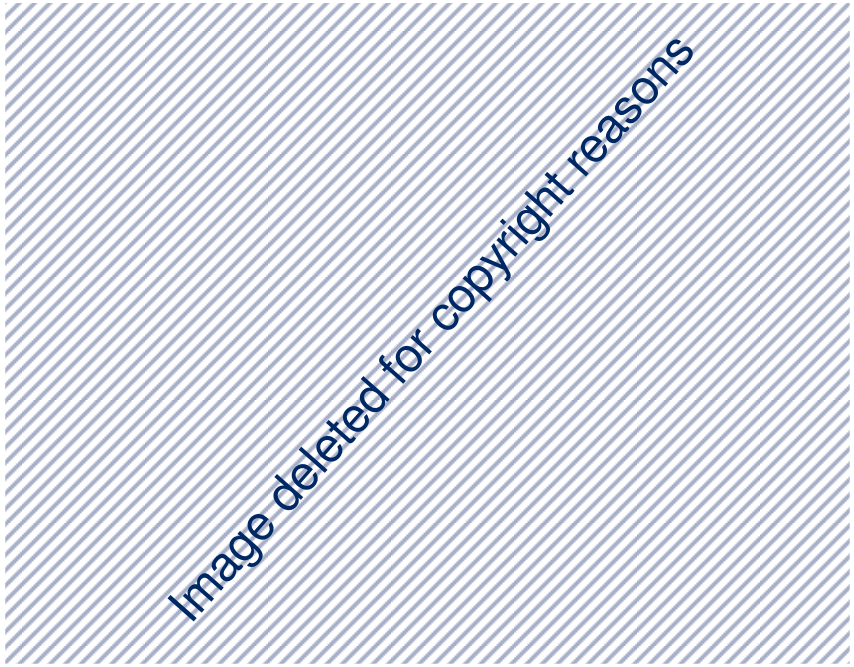
Autofluorescence pattern has prognostic character

Can changes of this pattern be considered as a short-term indicator of efficacy?

Holz et al. FAM-Study Group. ***Am J Ophthalmol 143:463-72, 2007***

Comparator Considerations

- No treatment for Dry AMD available
  - AREDS supplementation has slight effects only
- Suggested Comparators
  - Oral and topical drugs: Placebo w/ or w/o AREDS cocktail
  - Injectables: Sham injections w/ or w/o AREDS cocktail



The AREDS results show the slow course of onset of vision loss in dry AMD patients as well as the mild treatment effects of the AREDS medication.

Image from: AREDS report No. 8; Arch Ophthalmol (2001) 119:1417-36

Trial Duration

- Needs to be adapted to the endpoint variable
- Drusen Morphology[1)]
  - 3 to 6 Months (for PoC and Dose Finding)
  - 12 Months (for registration)
- GA lesion growth[2)]
  - 18 to 24 months (for registration)
- Autofluorescence pattern
  - 3 to 6 months (for PoC and Dose Finding; potentially for registration?)

Sources: 1) Landa G. et al. *J Ocul Pharmacol Ther* 27:77-82
2) Holz et al. FAM-Study Group. *Am J Ophthalmol 143:463-72, 2007*

Conclusion

- Visual acuity is not the preferred outcome measure for clinical development in dry AMD
- Morphological parameters have been developed recently and are under continuous evaluation and can be utilized as outcome variables soon