Presentation guidance

Session Topic	Clinician/academic view	Industry view	Regulatory view
Visual function	• Different aspects of visual function, e.g. visual acuity, contrast sensitivity, visual field, ERG, ERG, mircoperimetry, multifocal ERG, etc • Methods of analysis • In subjects with very poor vision, in children • What matters to the patient? • Relevant visual function endpoints in clinical trials pros and cons, validation status/ clinically meaningful differences	• Methods of analysis, 2 lines/ 3 lines, difference in mean change, • In subjects with very poor vision, in children • Endpoints in clinical trials • Interpretation – clinically relevant effects	• Endpoints in clinical trials • In subjects with poor vision • Interpretation – clinically relevant effects • Examples

Visual function endpoints
Industry view

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Topics outline

- Patient/ industry/healthcare perspective of visual function benefit
- Visual function*:
  - Methods of analysis, 2 lines/ 3 lines, difference in mean change.
  - Visual function evaluation in subjects with very poor vision, in children.
  - Endpoints in clinical trials.
  - Interpretation – clinically relevant effects.

* Focus of presentation on Visual Acuity (VA), as a key measure of macular visual function. Evaluation method of VA referred throughout - Best Corrected Visual Acuity (BCVA) using standard Early Treatment of Diabetic Retinopathy Study (ETDRS)-like charts of patients` examination.

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Visual function benefit...

- In patients` perspective:
  - to improve symptoms of visual function loss (distance and near visual acuity, contrast sensitivity, color vision function, peripheral vision, sharpness)
  - to maintain and/or regain quality of life dependent on visual functions, while under a medical/surgical treatment

  => at individual patient level

- In industry`s perspective:
  - to demonstrate efficacy in terms of affecting the symptoms of visual function loss
  - to demonstrate safety of the treatment

  => an overall favorable, positive benefit/risk profile of a treatment better than current therapy

  - But also:

    -clinical practice applicability of a demonstrated drug profile

    -access of patients/ clinical community to the treatment (market access, reimbursement)

    -impact on quality of life (health economics vs. comparator)

- In healthcare systems` perspective:
  - benefit of treatment vs. burden at individual/group patient level
  - impact on populational health (population health economics, avoidance of associated concomitant diseases and healthcare burdens)

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Methods of analysis

``*Loss of less than XX letters*`` @ 24mo vs. Baseline (BSL)

- Historically, due to the natural, chronic disease progression to visual acuity (VA) loss in macular conditions:
  - Efficacy outcomes: primarily analysed the ``*avoidance of VA loss*``: proportion (%) of subjects with ``loss of <15 letters``, no loss (i.e. ± 5 letters)
  - The outcome benefit: evaluated at a pre-determined primary/secondary timepoint compared to baseline, i.e. 12/24 months vs. baseline
  - An average outcome of >50% patients avoiding loss was considered clinically relevant compared to natural progression

TAP (A and B Combined) — All Lesions
1- and 2-Year Results

All Lesions*	Study Year 1 Visudyne (n=402)	Study Year 1 Placebo (n=207)	Study Year 1 Diff	Study Year 2 Visudyne (n=402)	Study Year 2 Placebo (n=207)	Study Year 2 Diff
Loss of <15 letters, %†	61.2	46.4	14.8%	53.0	37.7	15.3%
	P<0.001			P<0.001		
Loss of <30 letters, %	85.3	76.3	9.0%	81.8	70.0	11.8%
	P=0.006			P<0.001		
Gain of ≥15 letters, %	6.0	2.4	3.6%	9.0	3.9	5.1%
Mean VA change from baseline (letters)	–11.2	–17.4	6.2	–13.4	–19.6	6.2

* Intent-to-treat population with LOCF
† Primary endpoint

TAP Study Group. *Arch Ophthalmol.* 1999;117:1329–1345.
TAP Study Group. *Arch Ophthalmol.* 2001;119:198–207.

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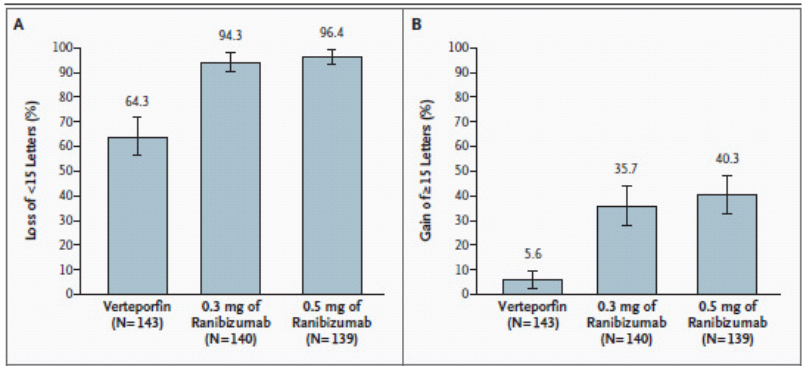
Methods of analysis
``*Gain of VA*``

- With recent pharmacological breakthroughs (eg intravitreal anti-VEGF treatment) for treatment of macular diseases that are the major cause of visual function (VA) loss:
  - Efficacy outcomes: primarily analysing the ``*VA gain*``: mean VA change, proportion (%) of subjects with ``gain >0, 5,10, 15 letters``

    (Brown et al., N Engl J Med 2006)



  - The outcome benefit evaluated at a primary/secondary timepoint compared to baseline (12/24 months), but also overtime (change over time)
  - An average outcome of avoidance of VA loss is no longer considered a relevant benefit (>90% of patients can avoid loss of >15 letters) when compared to previous therapies → VA gain has become the clinically relevant outcome

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The average ``VA gain`` as clinically relevant outcome

- Mean change in VA *at Month 12* compared to BSL: average of 10 letters (2 lines) gained at Month 12 with treatment
  - A natural and efficient summary measure for a continuous variable as the VA score *(Csaky et al., IOVS 2008)*
  - Difference in mean VA change between compared treatments: on average of 10-20 letters (2-4 lines)
    Brown et al., N Engl J Med 2006
- Proportion of patients with VA gain >10 letters, >15 letters (>2/3 lines) at Month 12: >40%
  - Difference between treatments: on average 2-3 fold

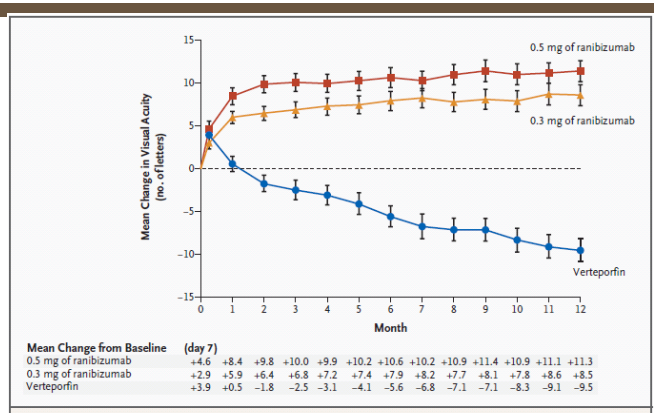
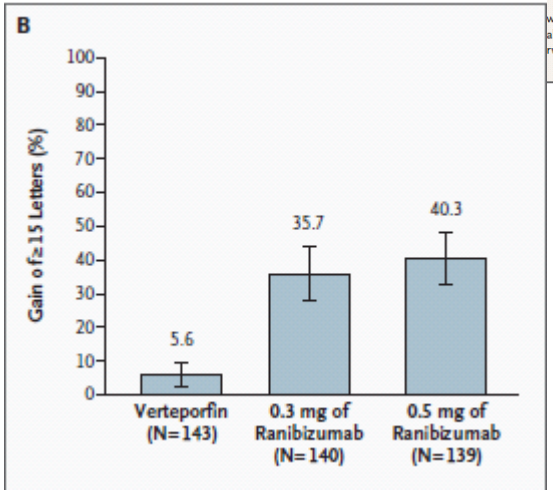


Figure 2. Mean (±SE) Changes in the Number of Letters Read as a Measure of Visual Acuity from Baseline

wise analysis of variance
alyze the mean change in
rward method was used to



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``VA gain`` endpoint analysed over time

- Mean change in VA *over time* compared to BSL: the average of each timepoint mean VA change → ``mean average VA change``
  - Evaluates the benefit outcome over the entire observation period with:
    - the variability between visits
    - the onset of benefit immediately after treatment initiation

Massin et al., Diabetes Care 2010

Mitchell et al., Ophthalmol 2011

Table 1—*Mean BCVA and CRT at month 12*

	Ranibizumab pooled	Sham
N	102	49
BCVA (ETDRS letters)		
Baseline	60.2 ± 9.9	61.1 ± 9.0
Mean average change from baseline to month 1 through month 12		
Average month 1 to month 12	68.0 ± 11.7	61.0 ± 13.9
Average change from baseline	7.8 ± 7.7	−0.1 ± 9.8
Comparison vs. sham		
Difference in least squares means	7.9	—
95% CI for difference	5.0 to 10.9	—
P value	<0.0001	—

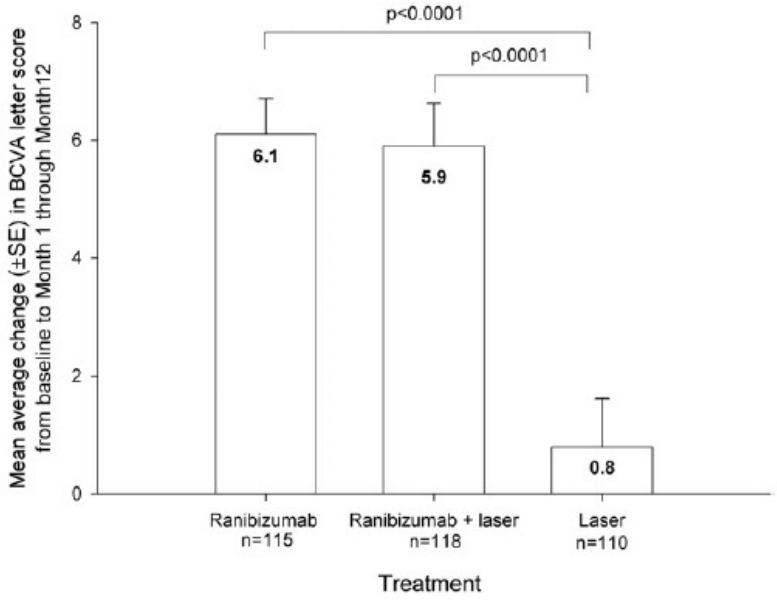

Figure 3. Mean average change in best-corrected visual acuity (BCVA) letter score from baseline to months 1 through 12 (primary end point). SE = standard error.

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Visual function evaluation in subjects with very poor vision, in children

- Standard ETDRS-like charts and BCVA protocols are not fully suitable for assessment of poor level VA, ie Count Fingers(CF), Hand Motion (HM)
- ETDRS and Snellen charts in poor agreement in patients w VA less than 20/200 *(Falkenstein et al., Ophthalmol 2008)*
- Assessment of function relies heavily on clinical and paraclinical evaluations
- Children younger than that of reading age – lack of standardised charts

  - Electroretinography (ERG), microperimetry as options to assess physiopathology of visual function?
  - Adaptive Optics (AO) an option to assess the rate of photoreceptors loss in conjunction with other tests?

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Clinical benefit assessments/endpoints today

Assessments	Endpoint	Comment
Visual acuity (VA)	Improvement in VA: Mean VA change *at* time Mean average VA change *over* time % VA gain >0, >5, >10, >15 letters % with VA >20/40 *at* time x	Snellen or other VA charts in clinical practice
Contrast sensitivity (CS)	Improvement in CS	Pelli-Robson charts not sufficiently standardised and calibrated, subjective
Reading performance	Improvement. Exploratory	Subjective, good technician/ reproducible methodoloy to achieve desired outcomes
Macular edema (Central retinal thickness, CRT, volume, CRV)	Reduction of edema: Mean CRT change Excess reduction	Function (BCVA)-anatomy (CRT) correlation not demonstrated; but new technology + testing edema as predictor of future VA loss. Evaluate photoreceptors health and amount of healthy retina.
Patient-reported visual function (VFQ-25)	Increase in VFQ-25 score	Correlation of VA gain w improvement in VFQ-25 scores in macular diseases; utility as measures of function loss *(Cusick et al., AJO 2005; Mangione et al., Arch Ophthalmol 2001)*

Csaky et al., IOVS 2008

Endpoints in clinical trials: desirable characteristics

- Measure a clinically relevant characteristic of disease progression to...
- Enable the demonstration of efficacy/ benefit with the treatment administration on the symptom of visual function loss, on average...
- And relevant to individual patients affected by the symptom...
- And ultimately applicable/replicable in standard clinical practice to benefit individual patients management with treatment

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Supportive assessments & endpoints: the function-anatomy hypothesis

The histopathologic characteristics that cause the visual function loss ``surrogate`` marker of the functional loss and its characteristics

- The use of retina/choroid imaging to indirectly assess the tissue affecting the visual function loss (i.e. describe type, predict the progression of function loss)
- Co-endpoints? → VA vs. Optical Coherence Tomography (OCT) debate

  → correlation function-anatomy to be demonstrated (high definition [HD], quantitative and qualitative)

  → VA vs. HD-OCT *or* microperimetry vs. HD-OCT? to determine function-anatomy correlation

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BCVA vs. CRT (studies of Diabetic Macular Edema)

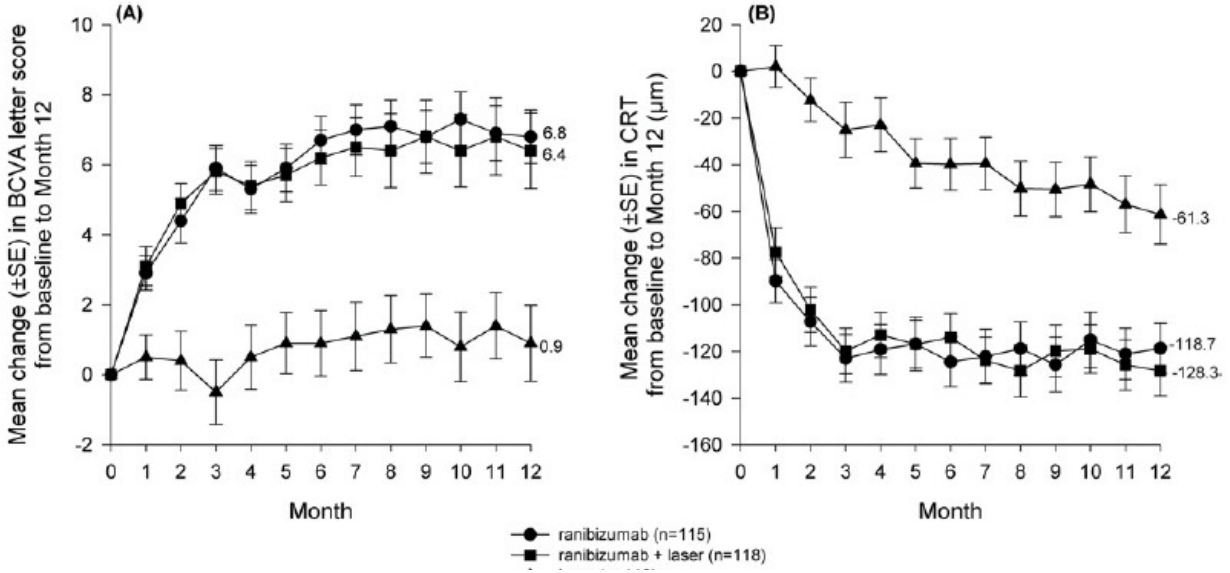
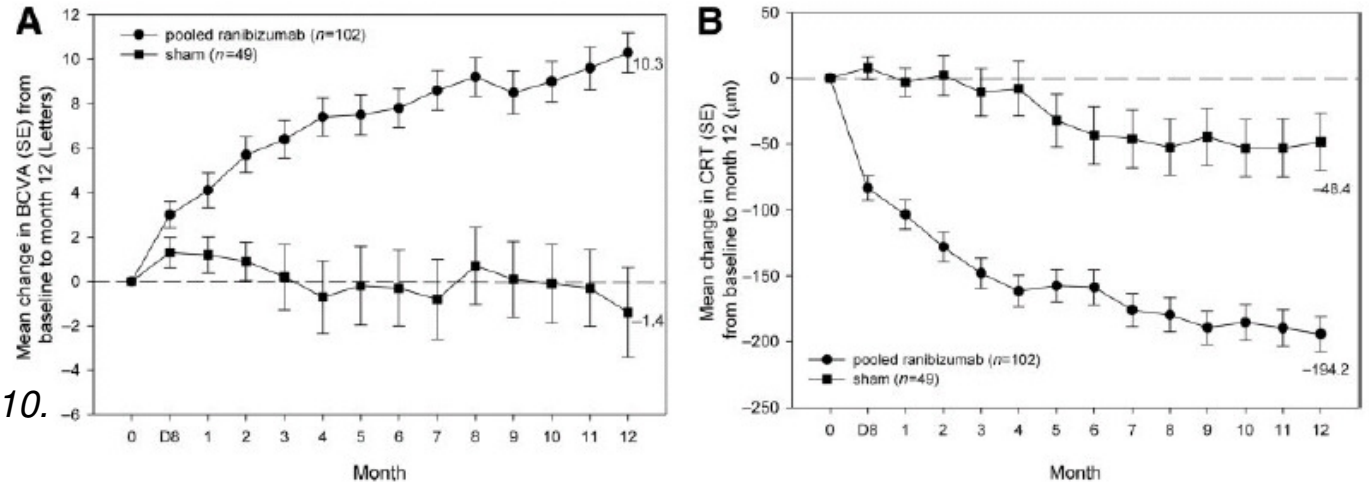


Figure 4. A, Mean change in best-corrected
(CRT) from baseline to month 12. SE = st



Massin et al. Diabetes Care 2010.

Mitchell et al. Ophthalmol 2011.

Figure 1—*Mean change from baseline to month 12 in (A) BCVA and (B) CRT of the study eye: data for pooled ranibizumab doses (0.3–0.6 an 0.5–1.0 mg) versus sham. Full analysis set, LOCF. (Ranibizumab by-dose data are found in supplementary Fig. 4A and B, available in an onlin appendix.)*

Interpretation of clinical relevance

1. The balance between magnitude of efficacy and the risk of having or not the treatment

2. Relevance *vis à vis* patient reported visual function (i.e. patient-reported outcomes – National Eye Institute (NEI) standardised Visual Function Questionnare (NEI VFQ-25) – a tool providing reproducible and valid data when used across multiple conditions of vaying severits *(Mangione et al., Arch Ophthalmol 2001)*

   → A gain of 10 or more letters leads to an increase in the composite NEI-VFQ-25 scores by an amount judged to be clinically significant in diseases of the macula (*Bressler et al., Arch Ophthalmol 2009; Chang et al., Arch Ophthalmol 2007; Mangione et al. 2001)*

3. Relevance *vis à vis* histopathological ``surrogate marker`` evidence (predictive HD-OCT co-endpoint) → moving into qualitative OCT assessments?

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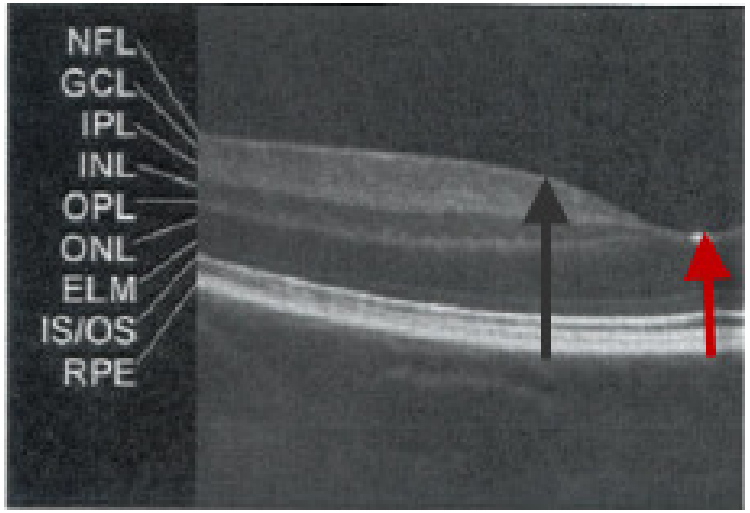
New high resolution technology: possible to evaluate qualitatively the individual layers and their interface morphology...

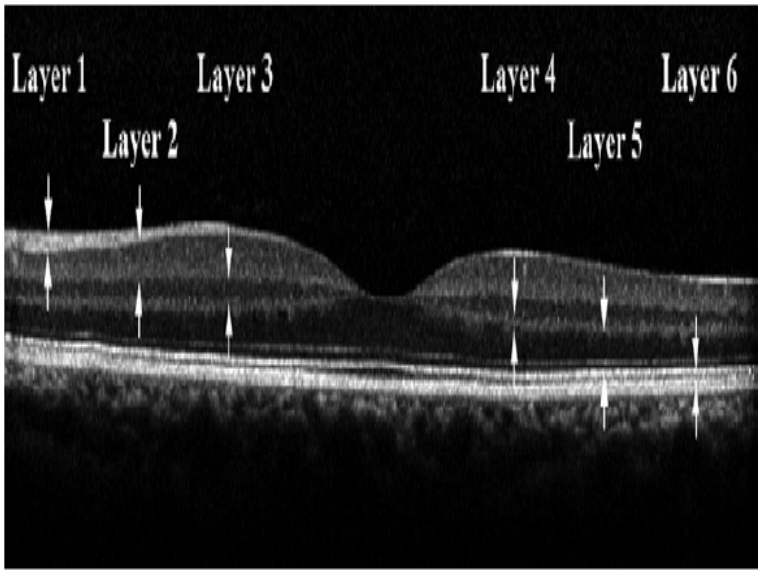
... with corresponding descriptive parameters, such as type, location, relation w adjacent layers

→further understanding of the pathophysiology of function loss



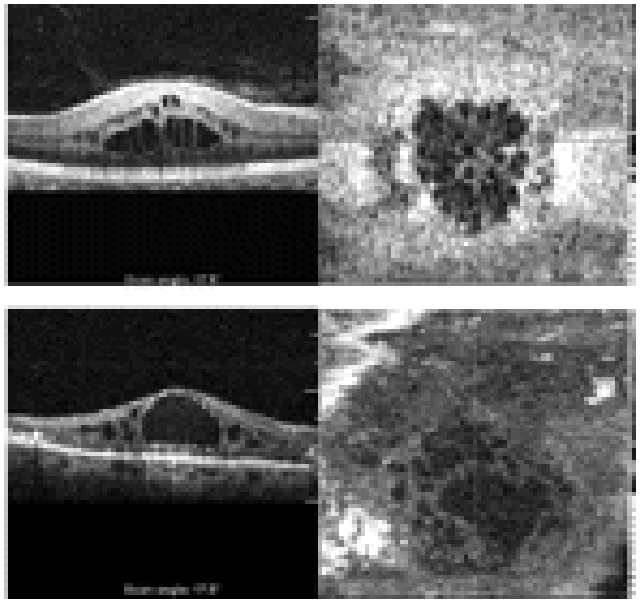
For example:

- Cysts presence/absence
- Fluid presence/absence
- Fibrosis presence/absence
- Vitreomacular interface, presence of traction
- Photoreceptors layer
- RPE/BM interface integrity/ disruption
- IS/OS interface integrity/ disruption

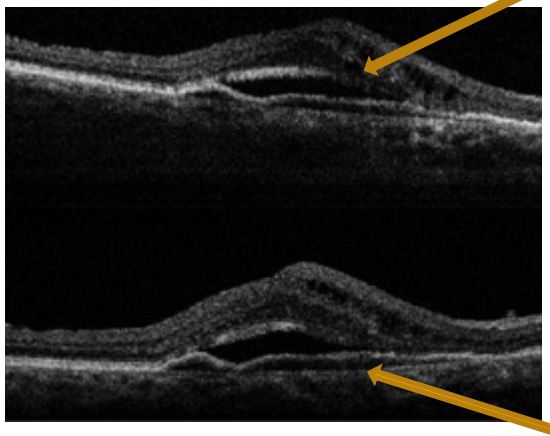


Qualitative anatomical OCT imaging parameters - predictive of the VA and functional changes?

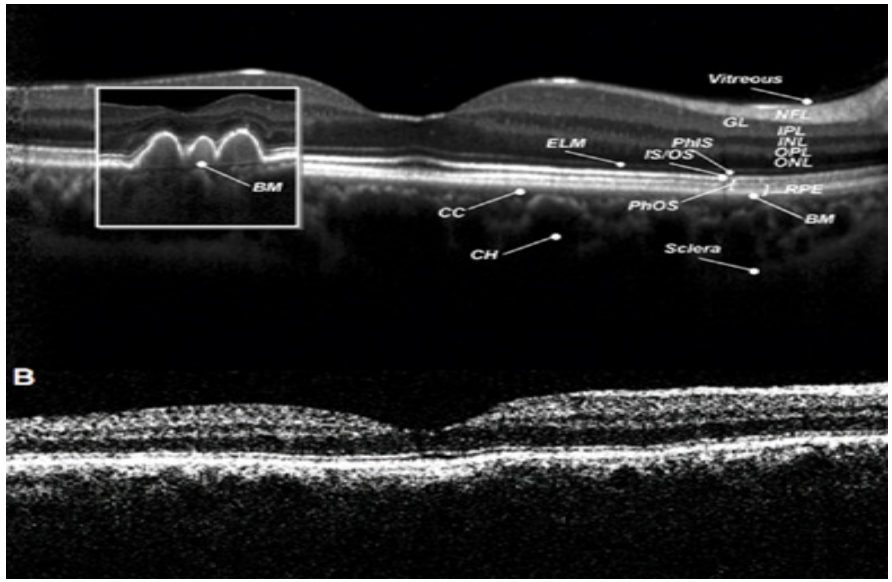
Cysts



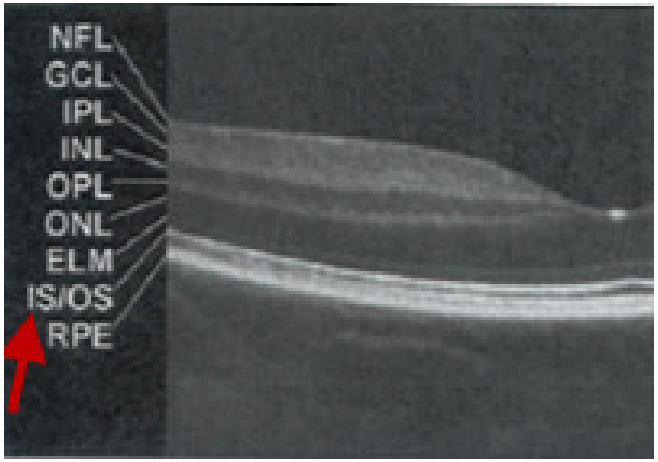
Intra/sub-retinal fluid



Integrity of RPE/MB



Integrity of IS/OS



What about the clinical relevance and clinical applicability of other visual function assessments? Is there a future?

- Multifocal ERG
- Microperimetry/ automated perimetry
- Contrast sensitivity with high spatial resolution
- Visual field (even for macula diseases that affect periphery)
- Scotopic sensitivity
- Color vision testing
- Dark adaptation
- Scotoma evaluation central/ peripheral

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Summary

- Patient/ industry/healthcare perspective of visual function benefit
  - Achieving outcomes of benefits relevant from all perspectives, but ultimately for individual patients is challenging
- Visual function:
  - Methods of analysis, 2 lines/ 3 lines, difference in mean change.
    - Evaluation of the treatment benefit overtime (mean average VA change), offers an overall more comprehensive assessment immediately after treatment initiation
  - Visual function evaluation in subjects with very poor vision, in children.
    - Standardised methods remain a challenge, globally
  - Endpoints in clinical trials.
    - Co-endpoints: primary endpoints w supportive surrogate markers are needed to better assess the overall benefit achieved in individual patients
  - Interpretation – clinically relevant effects.
    - Improvement in VA is the new aim, quantifying what is a relevant benefit in the average study population that translates significantly at the individual patient level needs further evaluation
    - Are predictive endpoints/biomarkers of disease progression/function loss valuable?

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