## Presentation guidance

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

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1 | Presentation Title | Presenter Name | Date | Subject | Business Use Only
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.
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)
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

<table>
<thead>
<tr>
<th></th>
<th>Study Year 1</th>
<th>Study Year 2</th>
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<tbody>
<tr>
<td></td>
<td>Visudyne (n=402)</td>
<td>Placebo (n=207)</td>
</tr>
<tr>
<td>Loss of &lt;15 letters, %</td>
<td>61.2</td>
<td>46.4</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td></td>
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<tr>
<td>Loss of &lt;30 letters, %</td>
<td>85.3</td>
<td>76.3</td>
</tr>
<tr>
<td></td>
<td>P=0.006</td>
<td></td>
</tr>
<tr>
<td>Gain of ≥15 letters, %</td>
<td>6.0</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>P=0.001</td>
<td></td>
</tr>
<tr>
<td>Mean VA change from baseline (letters)</td>
<td>-11.2</td>
<td>-17.4</td>
</tr>
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</table>

* Intent to treat population with LOCF
† Primary endpoint
Methods of analysis
``Gain of VA``

- With recent pharmacological breakthroughs (e.g., 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``


  - 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
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)  

- 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
``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
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?
# Clinical benefit assessments/endpoints today

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Endpoint</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity (VA)</td>
<td>Improvement in VA:</td>
<td><strong>Snellen or other VA charts in clinical practice</strong></td>
</tr>
<tr>
<td></td>
<td>Mean VA change at time</td>
<td></td>
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<tr>
<td></td>
<td>Mean average VA change over time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% VA gain &gt;0, &gt;5, &gt;10, &gt;15 letters</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% with VA &gt;20/40 at time x</td>
<td></td>
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<tr>
<td>Contrast sensitivity (CS)</td>
<td>Improvement in CS</td>
<td><strong>Pelli-Robson charts not sufficiently standardised and calibrated, subjective</strong></td>
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<tr>
<td>Reading performance</td>
<td>Improvement. Exploratory</td>
<td><strong>Subjective, good technician/ reproducible methodology to achieve desired outcomes</strong></td>
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<tr>
<td>Macular edema (Central retinal thickness, CRT, volume, CRV)</td>
<td>Reduction of edema:</td>
<td><strong>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.</strong></td>
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<tr>
<td></td>
<td>Mean CRT change</td>
<td></td>
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<td></td>
<td>Excess reduction</td>
<td></td>
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<tr>
<td>Patient-reported visual function (VFQ-25)</td>
<td>Increase in VFQ-25 score</td>
<td><strong>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)</strong></td>
</tr>
</tbody>
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*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
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
BCVA vs. CRT (studies of Diabetic Macular Edema)

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


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 Questionnaire (NEI VFQ-25) – a tool providing reproducible and valid data when used across multiple conditions of varying severities (*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?
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

Above RPE

Below RPE

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
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?