Visual Function Endpoints
The Regulatory Perspective

Jane Moseley
EMA Scientific Advice
27 October 2011 EMA Ophthalmology Workshop

© European Medicines Agency, 2011. Reproduction is authorised provided the source is acknowledged.
Disclaimer

The views presented are those of the individual and may not be understood or quoted as being made on behalf of the EMA or reflecting the position of EMA or one of its committees or working parties

No conflict of interest
The Regulatory Perspective

- Guidelines
- Scientific Advice
- Centralised procedures
- HTA / SA parallel - early development
- Globalisation FDA parallel SA
- Novel method/Bio-markers
CHMP Ophthalmology Guidelines
CHMP Ophthalmology Guidelines

No CHMP dedicated to ophthalmic conditions

Ophthalmology Mentioned:

- Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus Draft CPMP/EWP/1080/00 Rev. 1
- CPMP/EWP/2455/02 Clinical Development of Medicinal Products for the Treatment of Allergic Rhino-conjunctivitis
- CPMP/EWP/QWP/1401/98 Rev. 1 Investigation of bioequivalence
- CPMP/EWP/239/95 final Note For Guidance On The Clinical Requirements For Locally Applied, Locally Acting Products Containing Known Constituents
- CPMP/EWP/422/04 Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis
General guidelines

Selected guidelines for special mention

- CPMP/EWP/2330/99 Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study
- CHMP/EWP/83561/2005 GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS
- EMEA/CHMP/EWP/692702/2008 Extrapolation of results from clinical studies conducted outside Europe to the EU-population
- CHMP/EWP/2459/02 Reflection Paper on Methodological Issues in Confirmatory Clinical Trials planned with an adaptive design
- CPMP/EWP/1776/99 Rev. 1 Guideline on missing data in confirmatory clinical trials
- CPMP/EWP/2158/99 Choice of a Non-Inferiority Margin
Endpoints; General Guidelines

- General Guidelines important e.g. ICHE8, ICHE9.. etc
- Consider
  - Clinical benefit endpoint vs Surrogate
  - Composite, Global, Co-primary endpoints
  - Detailed Specification of primary endpoint
  - Responder categorical vs continuous variable
  - Multiplicity and Missing data
Frame of reference

The organ

Structure → Function → Abilities

Organ → Person → Societal context

Parameters of Visual functions

Visual acuity
Visual field
Contrast sensitivity
Color vision
Dark adaptation

Function vision

Reading
Orientation, mobility
Activities of daily living
Visual communication
Visual job skills

Consequences

Vision-related Quality of life

Making, keeping friendships
Social skills
Self confidence, fear of falls
Coping skills
Asking for assistance

Environment
CHMP Ophthalmology Scientific Advice
CHMP SA Ophthalmology Procedures

CHMP SA Ophthalmology Procedures by Year

Year


N

0 2 4 6 8 10 12 14 16
CHMP SA Ophthalmology

Breakdown of SA procedures by Anatomical Therapeutic area

- Protocol assistance: 24%
- SME: 21%

SA Questions on Functional Endpoints by Anatomical Therapeutic area

- Uveitis: 9%
- PS: 31%
- IOP: 22%
- AS: 38%

Percentage with FE:

- AS: 33%
- IOP: 6%
- PS: 75%
- Uveitis: 100%
Visual fields

Rarely proposed as Primary Endpoint / Co-primary needs to be supported by

- Data on test-retest method reliability in the actual patient group, more information on the progression rate measured by this method, linear or not.
- Percentage of patients who will deteriorate during the study
- More information in order to assess the clinical relevance of the variable
- Feasibility and sensitivity in different patient subsets
- Definition of responder
Scientific quantification of the primary endpoint will need to be translated into clinical benefit. The Company should quantify the proportion of patients likely to benefit and the extent to which vision will be preserved to give an overall assessment of the magnitude of clinical benefit.

The maintenance of visual acuity is of primary importance to the patient therefore a defined decrease of best corrected visual acuity should be considered in the definition of treatment failure that is used for the primary endpoint.
Best Corrected Visual Acuity

- The percentage of patients who gained more than 15 letters of best-corrected ETDRS visual acuity (BCVA)
- Minimal clinically relevant improvement (perceived as such by patients) in this disease is around 10 letters.
- Difference between active and placebo on change in best corrected visual acuity (BCVA) from baseline.
- A clinically relevant treatment effect prespecified and well justified in terms of the treatment effect on ‘change in BCVA from baseline’ and in difference in proportions with visual acuity (VA) categories of gain/loss/no change.
- Sustained effect on change on BCVA over time.
- Other definitions of responders as secondary endpoint.
Mean vs Categorical Variable

While a responder analysis is acceptable as primary endpoint, it is noted that dichotomising a continuous variable will result in loss of information. Difference in mean change in the number of letters from baseline may provide more power to detect treatment effects. .. secondary analyses.

Difference in mean change in letters from baseline may be preferable as primary outcome measure in the planned non-inferiority studies as it could provide greater discrimination between treatments than ‘loss of less than 15 letters on the ETDRS chart compared to baseline’
Imputation based on last observation carried forward (LOCF) is a common approach but would not be appropriate for a progressive disease. Methods which avoid bias towards demonstration of non-inferiority should be presented. All single imputation methods have the potential to reduce variability and this should be accounted for in the range of sensitivity analyses presented.

Additional analyses should be available documenting the scale and impact of rescue treatment on the primary VA endpoint. Suitably conservative approaches to handle these data will be required. For the analysis of 6 month response rates, patients receiving rescue treatment should be considered non-responders.
Attributing scores to semi-quantitative acuity in patients with very poor vision

Best recovery of visual acuity per eye over baseline; best response

Best visual acuity per patient vs baseline; a clinically relevant endpoint for the individual of special importance

Better eye, or both eyes (Cluster or Average)
CHMP Ophthalmology Centralised MAA Procedures
<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>INNCommonName</th>
<th>MAA Year</th>
<th>Therapeutic area</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISTIDE</td>
<td>Cidofovir</td>
<td>1996</td>
<td>CMV retinitis</td>
</tr>
<tr>
<td>VITRASERT</td>
<td>Ganciclovir</td>
<td>1996</td>
<td>CMV retinitis</td>
</tr>
<tr>
<td>EMADINE</td>
<td>Emedastine</td>
<td>1998</td>
<td>Allergic conjunctivitis</td>
</tr>
<tr>
<td>PRODUCT X</td>
<td>INN1</td>
<td>x</td>
<td>Anterior segment</td>
</tr>
<tr>
<td>AZOPT</td>
<td>Brinzolamide</td>
<td>1999</td>
<td>IOP</td>
</tr>
<tr>
<td>VITRAVENE</td>
<td>Fomivirsen</td>
<td>1999</td>
<td>CMV retinitis</td>
</tr>
<tr>
<td>VISUDYNE</td>
<td>Verteporfin</td>
<td>2000</td>
<td>Wet AMD</td>
</tr>
<tr>
<td>EVOXAC</td>
<td>Cevimeline hydrochloride</td>
<td>2001</td>
<td>Sicca Syndrome.</td>
</tr>
<tr>
<td>LUMIGAN</td>
<td>Bimatoprost</td>
<td>2001</td>
<td>IOP</td>
</tr>
<tr>
<td>TRAVATAN</td>
<td>Travoprost</td>
<td>2001</td>
<td>IOP</td>
</tr>
<tr>
<td>PRODUCT Y</td>
<td>INN2</td>
<td>x</td>
<td>Anterior segment</td>
</tr>
<tr>
<td>OPATANOL</td>
<td>Olopatadine</td>
<td>2002</td>
<td>Allergic conjunctivitis</td>
</tr>
<tr>
<td>MACUGEN</td>
<td>Pegaptanib sodium</td>
<td>2005</td>
<td>Wet AMD</td>
</tr>
<tr>
<td>RETAAANE</td>
<td>Anecortave acetate</td>
<td>2006</td>
<td>Wet AMD</td>
</tr>
<tr>
<td>DUOTRAV</td>
<td>Travoprost/timolol maleate</td>
<td>2006</td>
<td>IOP</td>
</tr>
<tr>
<td>GANFORT</td>
<td>Bimatroprost/timolol</td>
<td>2006</td>
<td>IOP</td>
</tr>
<tr>
<td>VITRAGAN</td>
<td>Ovine hyaluronidase</td>
<td>2007</td>
<td>Vitreous Haemorrhage</td>
</tr>
<tr>
<td>LUCENTIS</td>
<td>Ranibizumab</td>
<td>2006</td>
<td>Wet AMD</td>
</tr>
</tbody>
</table>
## Centralised Procedures Ophth 2

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Year</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARXXANT</td>
<td>Ruboxistaurin</td>
<td>2007</td>
<td>DIABETIC RETINOPATHY</td>
</tr>
<tr>
<td>RETISERT</td>
<td>Flucinolone acetonide</td>
<td>2007</td>
<td>UVEITIS</td>
</tr>
<tr>
<td>AZARGA</td>
<td>Brinzolamide / timolol</td>
<td>2008</td>
<td>IOP</td>
</tr>
<tr>
<td>NEVANAC</td>
<td>Nepafenac</td>
<td>2007</td>
<td>POST CATARACT PAIN AND INFLAMMATION</td>
</tr>
<tr>
<td>YELLOX</td>
<td>Bromfenac</td>
<td>2011</td>
<td>POST CATARACT PAIN AND INFLAMMATION</td>
</tr>
<tr>
<td>VEKACIA</td>
<td>Ciclosporine</td>
<td>2008</td>
<td>VERNAL KERATOCONJUNCTIVITIS</td>
</tr>
<tr>
<td>OZURDEX</td>
<td>Dexamethasone</td>
<td>2010</td>
<td>VEIN OCCLUSION MACULAR ODEMA</td>
</tr>
<tr>
<td>LUVENIQ</td>
<td>Voclosporin</td>
<td>2010</td>
<td>UVEITIS</td>
</tr>
<tr>
<td>EYLEA</td>
<td>VEGF-TRAP</td>
<td>Ongoing</td>
<td>WET AMD</td>
</tr>
<tr>
<td>SAN IDEBENONE</td>
<td>Idebenone</td>
<td>Ongoing</td>
<td>LEBER'S OPTIC NEUROPATHY</td>
</tr>
<tr>
<td>PRODUCT C</td>
<td>INN3</td>
<td>x</td>
<td>ANTERIOR SEGMENT</td>
</tr>
<tr>
<td>XALATAN</td>
<td>Latanoprost</td>
<td>2010</td>
<td>IOP</td>
</tr>
</tbody>
</table>
Centralised Procedures Ophthalmology

Year of MAA validation

Therapeutic Area

Outcome of MAA

N

0
1
2
3
4
5


7%
30%
23%

AS
IOP
PS
Uveitis

30%
30%
40%
40%

Clinical Relevance: The mean visual acuity score showed a difference of < 2 letter in X dose group after X years of treatment. The clinical relevance of this is questioned and needs to be justified.

The clinical relevance of the new proposed indication, /The limited data available to support this indication since only one relatively small study on the target population is available,/The relationship between the chosen efficacy end-points of X and the development of X and the more clinically relevant parameter of long-term visual acuity,/The lack of evidence of long-term, clinically relevant benefit.

Change Improvement in X by itself is not considered as a sufficiently relevant endpoint. The benefits of the treatment translating into a need for an interventional procedure endpoint should be demonstrated – a change in the primary endpoint.
**Efficacy:** statistically significant effects of X on primary endpoints were shown only in one out of three confirmatory trials, and, even in this trial, findings were not consistent. A pooled analysis suggested efficacy on x endpoint, but was largely inconclusive regarding other variables.

In the pivotal non-inferiority 1-year study N, X dose/kg was compared with Y. The results of the primary efficacy analysis, based on visual acuity, did not support non-inferiority vs. active control.

**Safety:** Visual acuity is the most relevant overall outcome for the patient. For a considerable part of the test study population, the visual acuity outcome seems to be impaired. It is not clear to what extent this is due to disease/intervention.
Other Concerns: Vision Function Endpoints

- Low vision- floor effect: submit a subanalysis of patients of all treatment arms of the pivotal studies entering the study with a VA < 20/200, since the room for further visual deterioration seems limited, which could have an impact on the outcome of the primary endpoint.

- Justify the absence of other tests of visual function, such as contrast sensitivity, visual fields, or automatic perimetry? such as ERG

- To measure BCVA, ETDRS vs Bailey-Lovie chart for clarification.

- Different starting VA test distances and their respective implications for the results should be explained.

- Only one eye was to be treated, therefore no conclusion can be made with regard to efficacy and safety of x in the second eye...
In both pivotal studies, the LOCF principle was applied. It is consequently a concern that an initial improvement in vision is carried forward.

The various scales used in the studies standard and validated?

Health-related quality of life (HQL): provide results

Provide plots (with confidence intervals) of visual acuity over time from pivotal clinical studies

Subsequent to the change of the primary endpoint, no re-estimation of sample size/power calculations seems to have been performed accordingly. Possible impact?
CHMP – HTA Parallel Advice
Parallel HTA advice

Significant challenge today: new medicines do not reach the all patients, diverging development requirements

- Pilot process testing multi-stakeholder consultations in early-stage drug development

- To improve clarity and alignment among the stakeholders regarding what constitutes a medicine’s value and the evidence required to demonstrate that value most effectively

- Involves clinicians, health technology assessors (HTAs), patient representatives, payers, regulators and drug developers from e.g. France, Germany, Italy, the Netherlands, Sweden, UK and EMA

- Parallel input on questions of therapeutic value; at an early stage of development e.g. on comparators / design of trial and endpoints / measures to show added value

- HTA only questions of economic value deriving from therapeutic benefits
EMA – FDA Parallel Scientific Advice (PSA)
EMA – FDA Parallel Scientific Advice (PSA)

**Limitations** and **Benefits** of PSA

- Timelines linked to SAWP meetings; need for careful planning and coordination → contact EMA & FDA well in advance

- Separate not joint answers

- Awareness that PSA meetings can replace or be complimentary to key milestone FDA meetings

- Especially useful at early stages in development
  - In areas with no/limited guidance → easier to align

- If no formal PSA –> **several informal exchanges on SA** -
  - between EMA & FDA in ‘clusters’ (eg. Oncology) / **ad-hoc** FDA-EMA teleconferences on SA

- Overall PSA total since 2006: 17; inc 1 - Ophthalmology

- Informal interactions since 2009: 11 inc 2- Ophthalmology
CHMP– Qualification of Novel Methodologies
New regulatory procedure

**CHMP Qualification Opinion**

on the acceptability of a specific use of the proposed method (e.g. use of a BM) in a R&D context (non-clinical or clinical), based on the assessment of data, not product-specific

Qualification team, peer review, public consultation, publication

**CHMP Qualification Advice**

on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted, confidential

**Aims**

SAWP/CHMP early involvement in the design of the strategy

commitment to evaluate the data obtained from the agreed studies and to provide a Qualification Opinion / speed up drug development
Qualification of Novel Methodologies

ICH guideline E16
Genomic biomarkers related to drug response: context, structure and format of qualification submissions
Step 4

<table>
<thead>
<tr>
<th>DRAFT AGREED BY SAWP</th>
<th>27 February 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION</td>
<td>24 April 2008</td>
</tr>
<tr>
<td>END OF CONSULTATION (DEADLINE FOR COMMENTS)</td>
<td>30 June 2008</td>
</tr>
<tr>
<td>FINAL AGREED BY CHMP</td>
<td>22 January 2009</td>
</tr>
</tbody>
</table>

Transmission to CHMP: June 2009
Transmission to interested parties: June 2009
Deadline for comments: September 2009
Final adoption by CHMP: September 2010
Date for coming into effect: December 2010
Experience to date

Qualification opinion ILSI/HESI submission of novel renal biomarkers for toxicity

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreed by Scientific Advice Working Party</td>
<td>February 2010</td>
</tr>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>18 March 2010</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>31 July 2010</td>
</tr>
<tr>
<td>Adoption by CHMP</td>
<td>21 October 2010</td>
</tr>
</tbody>
</table>

Qualification opinion of novel methodologies in the predementia stage of Alzheimer’s disease: cerebro-spinal fluid related biomarkers for drugs affecting amyloid burden

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreed by Scientific Advice Working Party</td>
<td>January 2011</td>
</tr>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>20 January 2011</td>
</tr>
<tr>
<td>Released for consultation</td>
<td>10 February 2011</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>25 March 2011</td>
</tr>
<tr>
<td>Adoption by CHMP</td>
<td>14 April 2011</td>
</tr>
</tbody>
</table>

EMA Home > Regulatory > Human medicines >

Scientific advice and protocol assistance > Novel methodologies / biomarkers
Concluding Remarks

- Regulatory body of experience in ophthalmology products
- Centralised EU discussion on methodologies / MAAs
- Multiple opportunities for interactions on ophthalmology products
- No specific ophthalmology guidelines

- Clinical relevance essential
  - Chosen endpoint
  - Clinically significant treatment effect for benefit risk balance
- Possibilities
  - surrogate endpoint qualification through regulatory procedure
  - prospective centralised discussions regarding proposed development plans
Frame of reference

The organ -> The person
Structure -> Function | Abilities | Consequences
Organ | Person | Societal context

Parameters of Visual functions
Visual acuity
Visual field
Contrast sensitivity
Color vision
Dark adaptation

Task performance, Function vision
Reading
Orientation, mobility
Activities of daily living
Visual communication
Visual job skills

Vision-related Quality of life
Making, keeping friendships
Social skills
Self confidence, fear of falls
Coping skills
Asking for assistance