Visual Function Endpoints
The Regulatory Perspective

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EMA Scientific Advice

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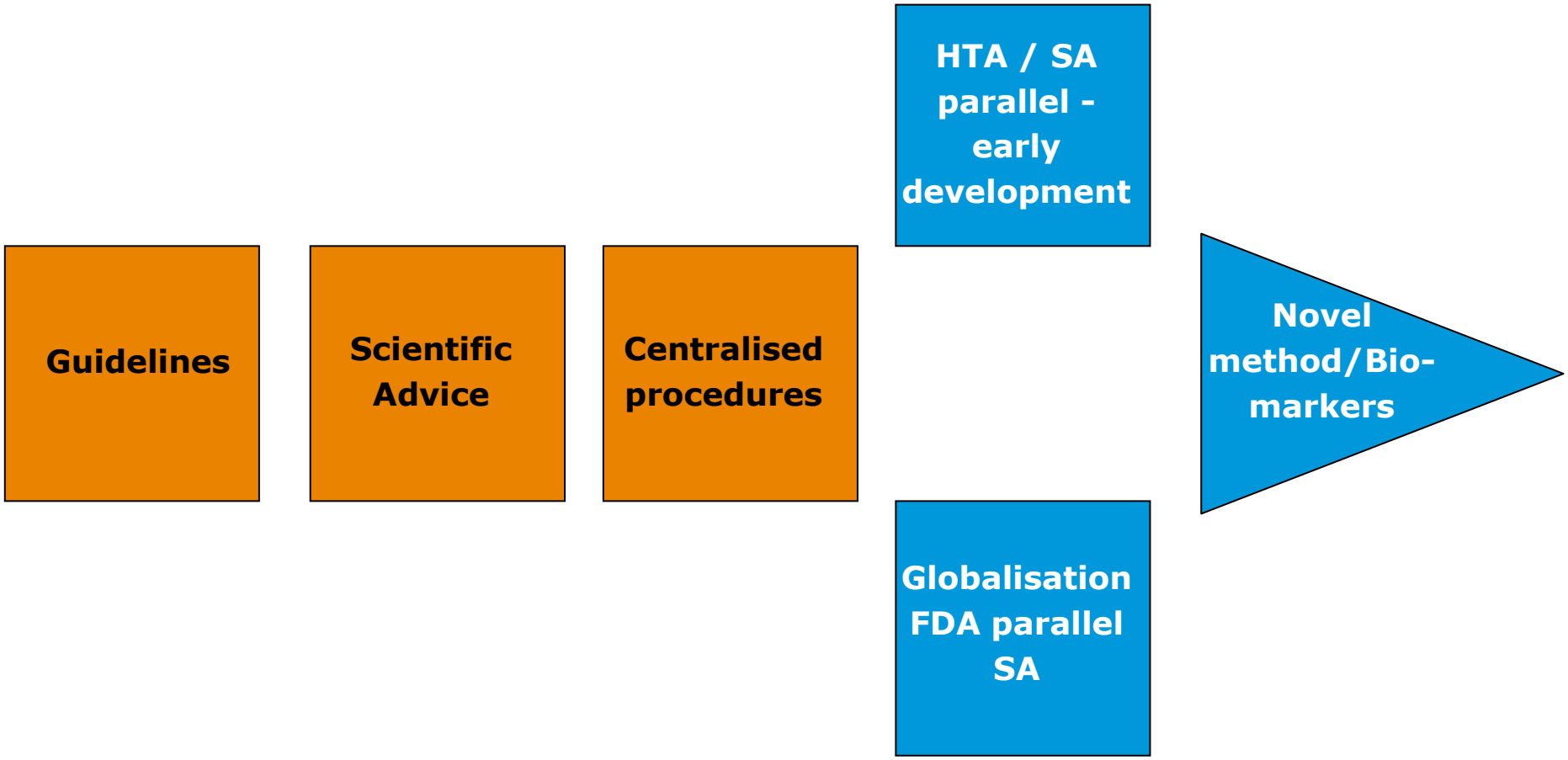
No conflict of interest

The Regulatory Perspective



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

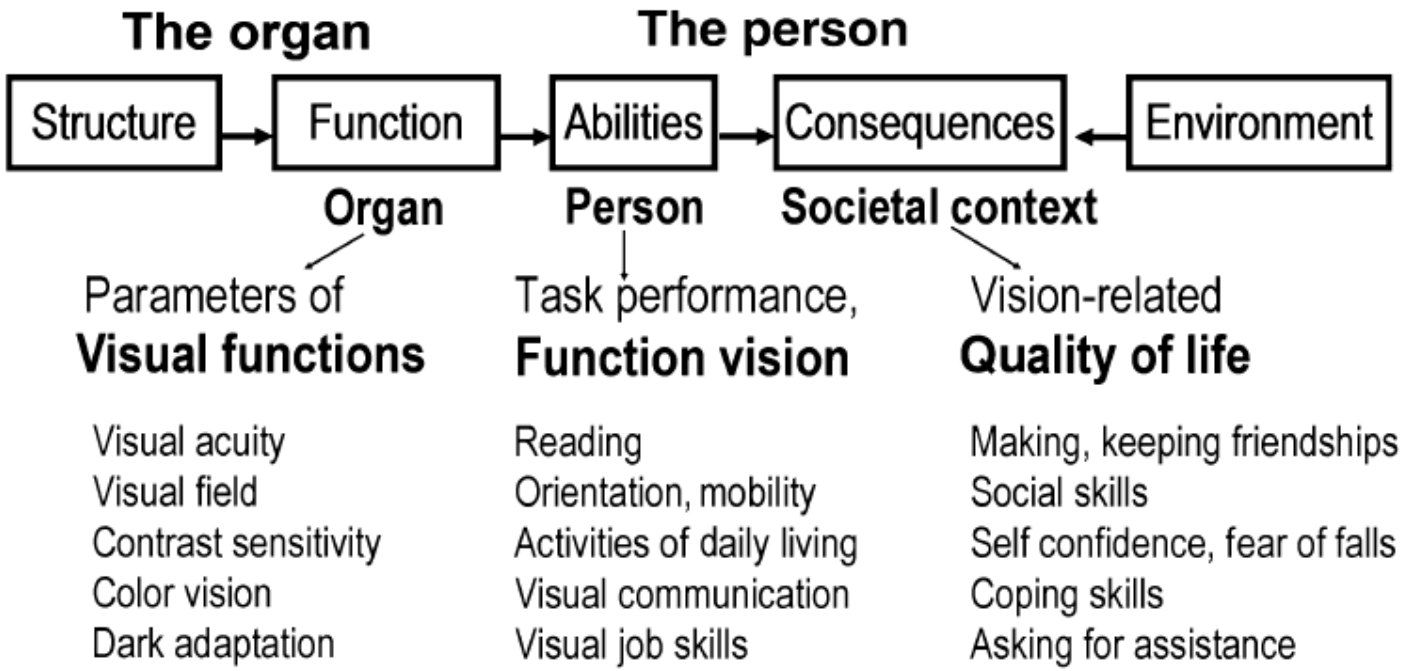
Selected guidelines for special mention

- 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
- CPMP/EWP/139391/04 Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal products

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

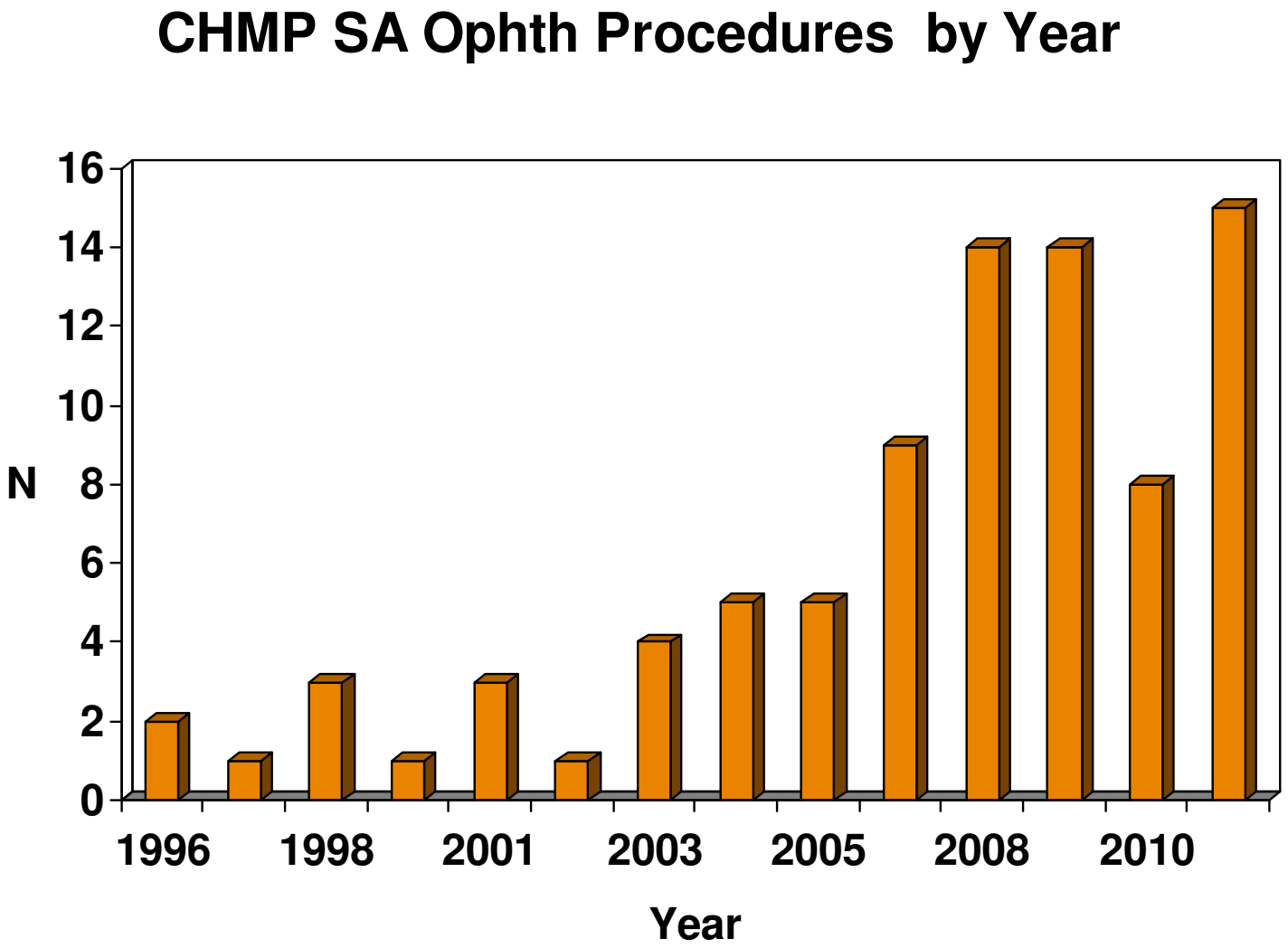
Frame of reference



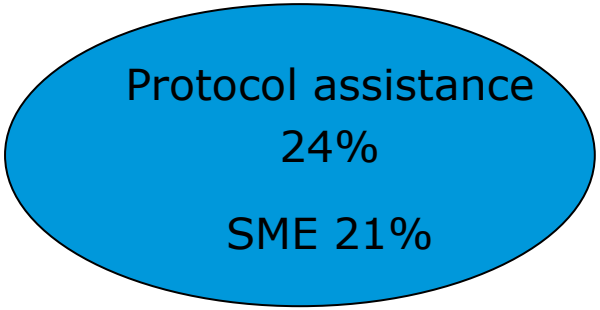
Acta Ophthalmol. 2010 Mar;88(2):163-73. Epub 2009 Dec 17.
Assessment of functional vision and its rehabilitation.
Colenbrander A
Reproduced courtesy of the author

CHMP Ophthalmology Scientific Advice

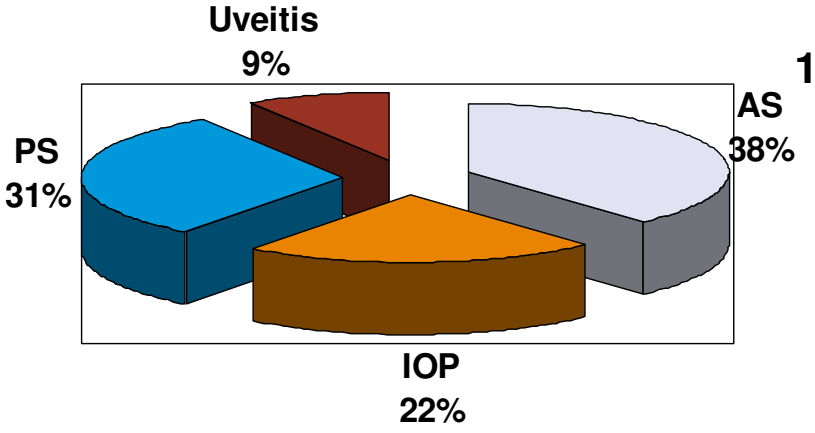
CHMP SA Ophthalmology Procedures



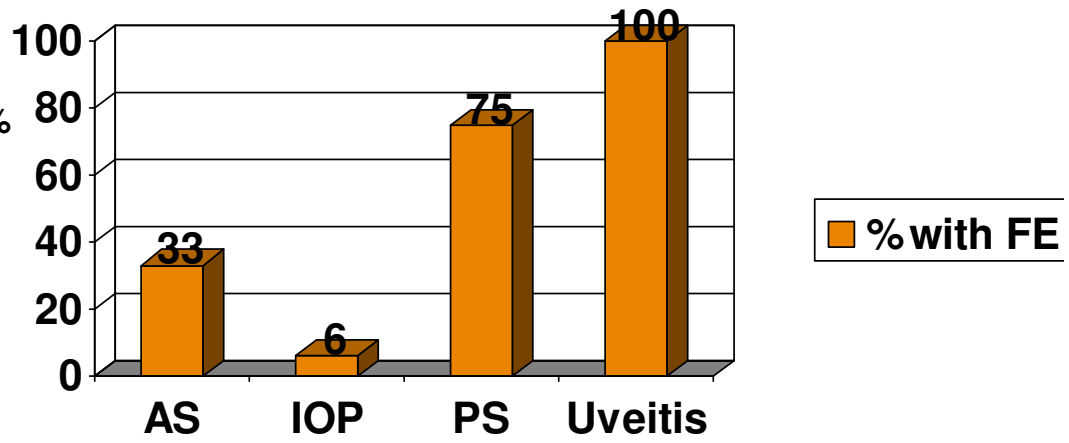
CHMP SA Ophthalmology



Breakdown of SA procedures by Anatomical Therapeutic area



SA Questions on Functional Endpoints by Anatomical Therapeutic area



EMA ophth Scientific Advice Vision Function Endpoints

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

Visual Acuity Emphasis

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'

VA Missing Data

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

Very Low Vision

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

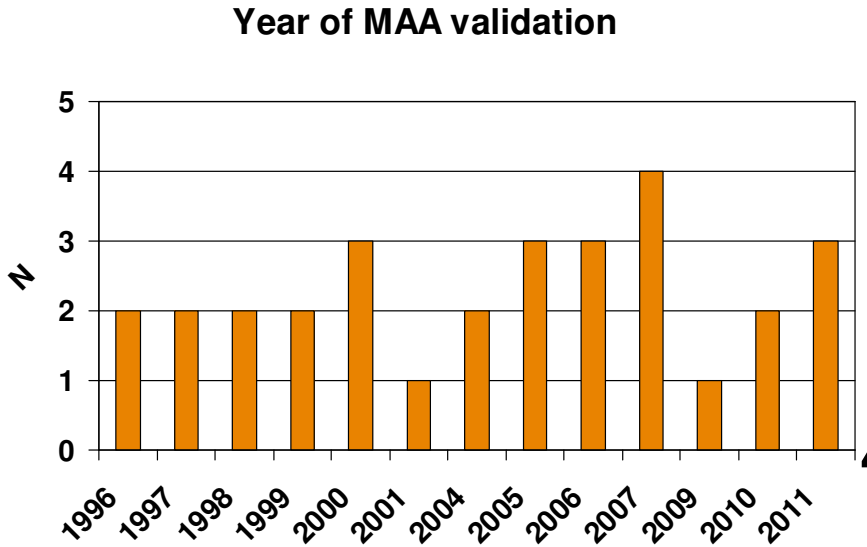
Centralised Procedures Ophth 1

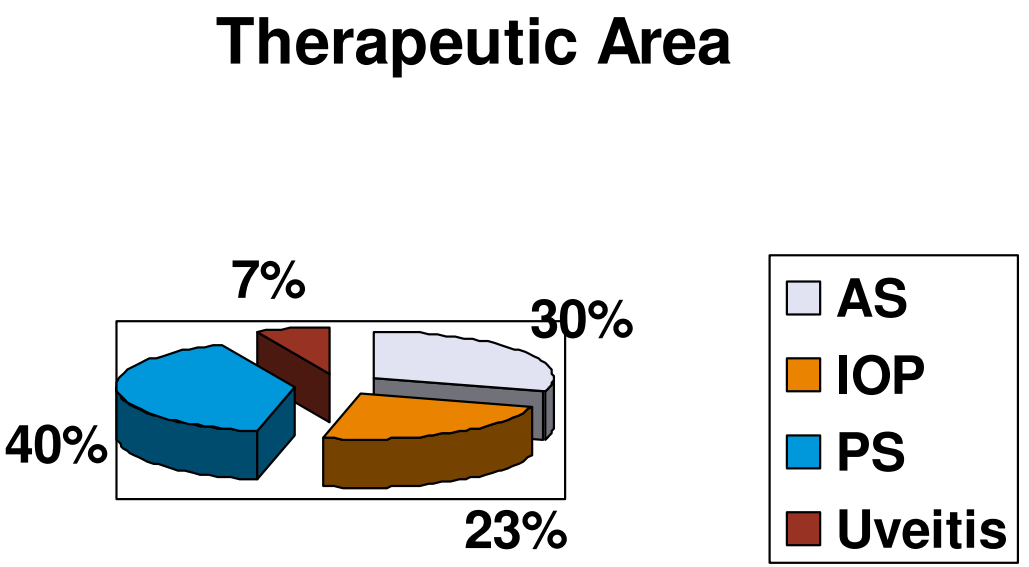
PRODUCTNAME	INNCommonName	MAA Year	Therapeutic area
VISTIDE	Cidofovir	1996	CMV retinitis
VITRASERT	Ganciclovir	1996	CMV retinitis
EMADINE	Emedastine	1998	Allergic conjunctivitis
PRODUCT X	INN1	x	Anterior segment
AZOPT	Brinzolamide	1999	IOP
VITRAVENE	Fomivirsen	1999	CMV retinitis
VISUDYNE	Verteporfin	2000	Wet AMD
EVOXAC	Cevimeline hydrochloride	2001	Sicca Syndrome.
LUMIGAN	Bimatoprost	2001	IOP
TRAVATAN	Travoprost	2001	IOP
PRODUCT Y	INN2	x	Anterior segment
OPATANOL	Olopatadine	2002	Allergic conjunctivitis
MACUGEN	Pegaptanib sodium	2005	Wet AMD
RETAANE	Anecortave acetate	2006	Wet AMD
DUOTRAV	Travoprost/timolol maleate	2006	IOP
GANFORT	Bimatroprost/timolol	2006	IOP
VITRAGAN	Ovine hyaluronidase	2007	Vitreous Haemorrhage
LUCENTIS	Ranibizumab	2006	Wet AMD

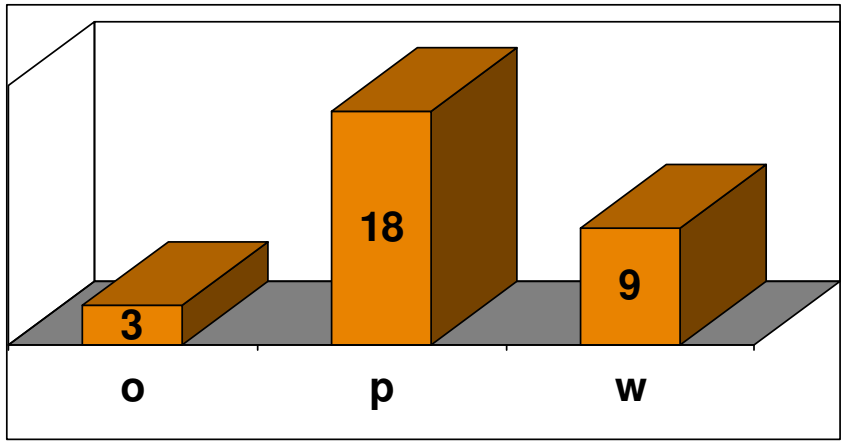
Centralised Procedures Ophth 2

ARXXANT	Ruboxistaurin	2007	DIABETIC RETINOPATHY
RETISERT	Flucinolone acetonide	2007	UVEITIS
AZARGA	Brinzolamide / timolol	2008	IOP
NEVANAC	Nepafenac	2007	POST CATARACT PAIN AND INFLAMMATION
YELLOX	Bromfenac	2011	POST CATARACT PAIN AND INFLAMMATION
VEKACIA	Ciclosporine	2008	VERNAL KERATOCONJUNCTIVITIS
OZURDEX	Dexamethasone	2010	VEIN OCCLUSION MACULAR OEDEMA
LUVENIQ	Voclosporin	2010	UVEITIS
EYLEA	VEGF-TRAP	Ongoing	WET AMD
SAN IDEBENONE	Idebenone	Ongoing	LEBER'S OPTIC NEUROPATHY
PRODUCT C	INN3	x	ANTERIOR SEGMENT
XALATAN	Latanoprost	2010	IOP

Centralised Procedures Ophthalmology







D120 Major Object'n Vision Function Endpoints

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.*

D120 Major Object'n Vision Function Endpoints

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 dosemg 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…

Other Concerns: Vision Function Endpoints

- 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

European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 22 January 2009
Doc. Ref. EMEA/CHMP/SAWP/72894/2008 Corr[1]

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

QUALIFICATION OF NOVEL METHODOLOGIES FOR DRUG DEVELOPMENT: GUIDANCE TO APPLICANTS

DRAFT AGREED BY SAWP	27 February 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 April 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 June 2008
FINAL AGREED BY CHMP	22 January 2009

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

September 2010
EMA/CHMP/ICH/380636/2009
Committee for medicinal products for human use (CHMP)

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

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

21 October 2010
EMA/CHMP/SAWP/283298/2010
Committee for Medicinal Products for Human Use (CHMP)

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

Agreed by Scientific Advice Working Party	February 2010
Adoption by CHMP for release for consultation	18 March 2010
End of consultation (deadline for comments)	31 July 2010
Adoption by CHMP	21 October 2010

14 April 2011
EMA/CHMP/SAWP/102001/2011
Procedure No.: EMEA/H/SAB/005/1/QA/2010
Committee for Medicinal Products for Human Use (CHMP)

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

Agreed by Scientific Advice Working Party	January 2011
Adoption by CHMP for release for consultation	20 January 2011
Released for consultation	10 February 2011
End of consultation (deadline for comments)	25 March 2011
Adoption by CHMP	14 April 2011

EMA Home >Regulatory > Human medicines >

Scientific advice and protocol assistance > Novel methodologies / biomarkers

Concluding Remarks

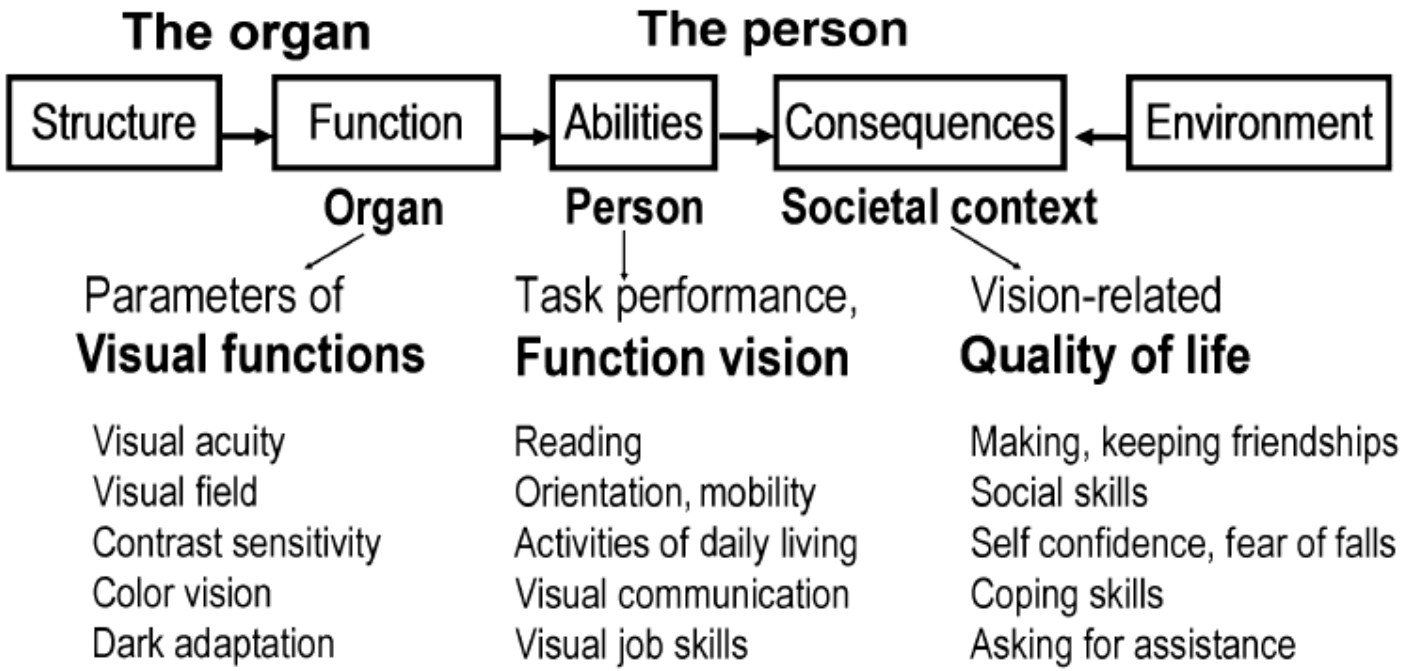
- Regulatory body of experience in ophthalmology products
- Centralised EU discussion on methodologies / MAAs
- Multiple opportunities for interactions on ophthalmology products
- No specific ophthalmology guidelines

- 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

EMA Home > Regulatory > Human medicines > Scientific guidelines

EMA Home >Regulatory >Human medicines > Scientific advice and protocol assistance

Frame of reference



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