Safeguarding public health

Regulation of products for Macular Oedema

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Points to be covered

- Length & number of studies
- Trial population
- Endpoints
- Comparators
- Combination therapies

- 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

Length & Number of Studies

Regulatory principle

- Study duration
  - Demonstration of sustained effect on endpoint
  - Requirement for long-term safety data (ICH E1)
- Number of studies
  - CPMP/EWP/2330/99
  - New product vs. variation to existing product

Length & Number of Studies

In general, 1 year efficacy and safety data from 2 studies are expected prior to approval

However, study duration is dependent on

- Robust demonstration of efficacy for recommended posology
- Current level of knowledge about drug class
- Duration of action of comparators
- Natural course of disease

- For example

  - Evidence exists for maintained effect of VEGF inhibition in DMO beyond 1 year (DRCR.net, READ-2)
  - The delayed effects of laser need to be factored into length of follow-up
  - In BRVO, some patients with macular oedema can be expected to improve spontaneously by 1 year

Length & Number of Studies

Other points to consider

RVO

- Follow-up should address risks of development of retinal ischaemia and neovascular complications

RVO/DMO

- Frequency of long term monitoring and retreatment, and potential for widening treatment interval

Number of Studies/Trial Population

Trial population should generally be heterogenous and should mirror target population

- RVO
  - Combined studies enrolling both BRVO & CRVO patients (Ozurdex) or separate studies for BRVO & CRVO patients (Lucentis)
  - Inclusion of patients with ischaemic RVO and diabetes
- DMO/RVO
  - Efficacy in newly diagnosed vs. chronic macular oedema

Endpoints

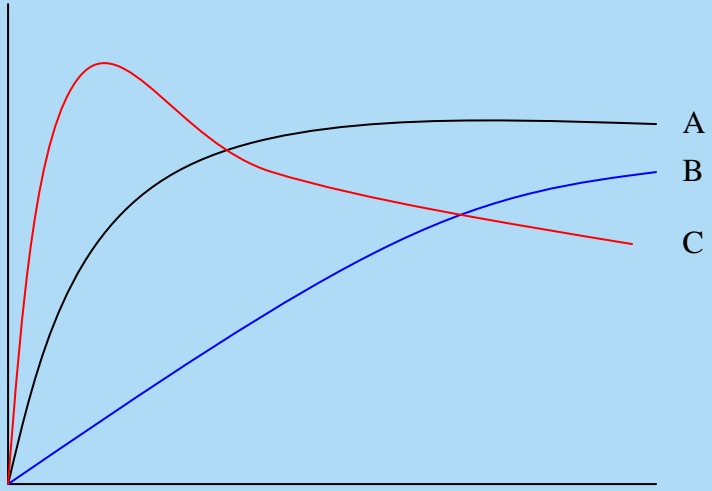
Regulatory principle

- Primary endpoint needs to reflect clinically relevant effect
- Methods for measurement of this endpoint should be accurate, precise, reproducible, reliable, and responsive
- Results for primary endpoint will be reviewed in the context of the overall findings of the clinical package

Endpoints

Primary

- Proportion gaining 15 letters
- Mean change in BCVA
- Mean average change in BCVA, AUC approach



Endpoints

Secondary

- Categorised change in BCVA
- Macular thickness
- Development of neovascularisation (RVO)
- Need for rescue therapy
- Progression/development of retinal ischaemia (RVO)
- Quality of life measure (NEI VFQ-25)

Other

- reduction in the frequency of rescue injections
- decrease in treatment burden (of combination therapy vs. monotherapy)
- regression of CNV

Endpoints

AMD

- Proportion maintaining vision (loss <15 letters)
  vs.
- proportion gaining vision, or mean change in vision

Comparators

Regulatory principle

- Placebo
  - Does licensed treatment exist?
  - Is it ethical to withhold this?
- Active control
  - Assay sensitivity
  - Safety outcomes

Comparators

RVO
- Licensed treatments: Lucentis, Ozurdex
- Alternative therapy: macular laser

DMO
- Licensed treatment: Lucentis
- Alternative therapy: macular laser

Other points
- Avastin
- Comparator regime

Combination therapies

‘Guideline On Clinical Development Of Fixed Combination Medicinal Products’

Advice on combination of medicinal products with procedures in this arena is uncharted territory…

- Length of follow-up
- Timing of treatments

Concluding remarks

- Rapidly changing therapeutic area, with several products under development
- Increasing prevalence of diabetes and RVO
- Need for therapies which offer improvements to vision with an acceptable risk profile and without an excessive burden on patients and clinicians
- Applications will ultimately be assessed on a case by case basis according to the benefit-risk profile.