Dry Eyes – Regulatory perspectives

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EU Regulatory Workshop – Ophthalmology
27-28 October 2011

The views presented are personal and not necessarily the views of the SAWP, the CHMP or the MPA
Give a regulatory view on frequently asked questions

- For example,
  - Study population
  - Endpoints
  - Comparator
  - Duration of studies
  - Adverse environment chamber
  - ...
No centrally approved pharmacological therapy in EU

- Approved (MRP)
  - Pilocarpine 5 mg tablets
    - Symptomatic treatment of dry eyes in Sjögren’s syndrome

- Used (SE)
  - Bromhexine 8 mg
  - Evening primrose (*Oenothera glazioviana*)
  - …

*Certain medicinal products for external use (specific for SE)*
Heterogeneous disease

• **Reason for dry eye?**
  – Impaired tear function, meibomian gland dysfunction (MGD), mucin deficiency, extrinsic factors, a mix

Evaporative

Tear deficient
Define target population!

- Reasons for dry eye
- Well-documented history of DED
  - Persistence of symptoms
- Severity
  - Reasonable to target a more severe population for pharmacological therapy
    - (Mild), moderate, severe?
    - Based on signs and symptoms

- Duration of disease
  - Affect corneal sensitivity (symptoms)?
  - Affect severity?
Endpoints - Requirements

• Which weight are they given?

• What are the associated claims?

• All data will be considered

• Benefits in relation to risks
Endpoints

• Signs and symptoms
  – Normally significant differences both in symptoms and signs required (co-primary endpoint)
  – Significant effect in sign or symptoms with a strong trend in the other
    • Multiplicity
Signs (I)

• **Consider target population**
  – Selection of one sign over the other guided by
    • disease aetiology
    • underlying mechanism of action of the compound
    • phase II data

• **Frequently used**
  – Corneal staining (Oxford, NEI)
    • Justify validity of other scales
  – Schirmer
  – Tear break up time
    • generally a secondary endpoint, of importance in MGD
Signs (II)

• **Upcoming**
  – Tear osmolarity
    • Option if supported with validated evidence
  – Ocular protection index?
    • Limited info

• **In MGD**
  – Appearance of lid margin abnormalities/redness and/or gland obstruction/drop out
    • Standardised grading and evaluation system not available
  – Composition of meibum?
Symptoms

• Symptomatic disease!

• Composite measure recommended
  – Validated questionnaire
  – MGD - no specific questionnaire available

• Use of one single worst symptom discouraged
  – Subjectivity and variability limit usefulness
    • Adequate marker of a subjective clinical benefit??
  – Changes in other symptoms may not parallel worst symptom over time
  – Multiplicity!
In addition

• Address the intended mode of action of the compound
  – Tear production
  – Marker of mucin secretion
  – Meibum composition
  – Marker of ocular surface inflammation
Effect size

• **Statistical significance not all...**
  – Relevant effect size!
  – The effects size needs to be supported for the chosen endpoint

• **Include evaluation of mean changes and responder analyses**
  – Difference between the means must be clinically relevant
  – Predefined relevant definition of responders
Comparator (I)

- **Vehicle**
  - Straight forward
  - Addresses potential effect/intolerance of vehicle

- **Artificial tears**
  - If target population already regular users (more severe population)
  - If composition of vehicle similar to what is included in artificial tears
Comparator (II)

- In MGD
  - Vs. best standard of care?
    - Best standard of care not defined
      - lid hygiene/warm compresses/lid massage
      - artificial tears/topical lipid supplements
      - (topical antibiotics/tetracycline p.o.)
  - Masking and compliance with lid hygiene an issue!
Concomitant use of artificial tears

- May be necessary to prevent a large drop-out (in vehicle group)
  - if infrequent administration

- Must be documented

- Address extent of use as a secondary outcome
Duration of studies

- **Pharmacological treatment**
  - **Efficacy**
    - When chronic treatment foreseen, primary evaluation at 6 months to confirm that effect is maintained
  - **Safety**
    - Generally 12 months (ICH E1 Population Exposure)
    - If (chronic) intermittent use foreseen, consider randomised withdrawal to evaluate maintenance.

- **Artificial tears**
  - If new composition, 3 months generally sufficient for efficacy.
  - Longer safety follow up needed.
Controlled adverse environment

- **Useful in exploratory trials**
  - Proof of concept
  - Aid in dose selection
  - Evaluate biomarkers

- **Not acceptable as pivotal trial without environmental study**
  - Selects an enriched patient population
    - Questioned whether this population is representative for target population
  - Lose real life heterogeneity
    - Overestimation of effect
Inflammation

- Several anti-inflammatory products in development
- Secondary manifestation
- Need to address in PD studies (biomarkers)
- Exploratory marker in pivotal studies
- Duration of effect after discontinuation of treatment?
Studies in general

• **Superiority trials**
  – Lack of comparator in EU
  – If available, assay sensitivity still an issue

• **History of failures, two confirmatory studies recommended**
  – Don’t have to be replicates
  – One pivotal trial
    • A clinically convincing and statistically compelling outcome needed (PtC One Pivotal study CPMP/EWP/2330/99)
In conclusion

• Sign & symptoms stage
• Need to learn more about the disease(s)
• Need to get a better understanding of
  – the relevance and usefulness of different outcome measures
  – the strengths and weaknesses of the symptom scales and visual function quality of life questionnaires
Thanks for your attention!!

Questions?