Intraocular Inflammation
Regulatory views

examples from SAWP and CHMP centralized procedures

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Scope

Regulatory views from the last 10 years

- proposals made by SAWP in Scientific Advice requests by companies
- issues raised during assessment of centralized procedures in CHMP
- [for PIPs see afternoon breakout session]

.. this presentation should not be seen as providing final answers, it rather aims at triggering further discussion on contentious issues

Which endpoints can be accepted?

Primary endpoints should be **clinically relevant**.

→ preference of visual function outcomes

*in Scientific Advice **VA** / **EDTRS** have been repeatedly proposed/accepted as primary, co-primary or key secondary endpoint*

However: this will depend on feasibility and treatment duration

- in disease stages with irreversible (chronic) visual damage improvement often can not be expected, but VA still relevant to examine possible further deterioration
- in short trials (acute disease) VA change might be less suitable as primary outcome, but still relevant secondary outcome
- expected change amplitude will have to be estimated for power calculation.
- as co-primary also often included in SUN criteria

Which endpoints can be accepted?

→ **SUN criteria** have also been accepted as surrogate

This could include the full parameter list or select only parts

Examples:

- **vitreous haze** (standard 5 unit scale (0-4+) has been accepted in an acute setting by SAWP (however with a preference for a primary endpoint at 4 wks rather than the proposed 6 wks)
- **anterior chamber cells** (5 unit scale) after 4 wks was not supported for moderate disease stages in a chronic setting, as not fully reflecting improvement (limited range of response)
- Possible as continuous measure or for ***recurrence definition***

  eg. visual haze & AC cell no ≤0.5 after 24 wks, with no increase ≥2 AC cells, ≥2 VH, no decrease ≥10 ETDRS within this period (the latter was considered too large)
- There is a need to exactly **specify the criteria to match** the included patient population (e.g. with regard to population homogeneitiy, disease severity & course of the disease)

Which endpoints can be accepted?

→ **corticoid-sparing outcomes** are also welcome in patients with need for continued steroid treatment

need to specify SOC, dosage range, steroid tapering regimen

e.g. proportion of patients receiving >10 mg corticosteroids was agreed, but higher dose (e.g. 25 mg/dy was preferred

Recurrence rates

- is considered relevant, but needs exact definition *(e.g. > 0.3logMAR ΔVA, specifed* VH and/or AC cell numbers etc)
- recurrence rate alone might **not cover** more harmful or **prolonged progression**
- **frequency of recurrences** preferred to **time to 1st recurrence** (especially with regard to demonstrating maintenance of effect in a confirmatory trial)

Supplementary information might include fluorescein angiography, optical coherence tomography, automatic perimetry threshold (Humphrey 24-2), etc

What is an appropriate trial duration?

This will depend on chosen endpoints and proposed label

Examples:

- for **chronic** / autoimmune uveitis trial durations of 24 weeks treatment + 12 wks saftey FU have beene accepted (16 weeks treatment was considered too short)
- 24 weeks incl safety FU has been accepted for a line extension with other indications already approved
- vitreous haze (5 unit scale) after 16 weeks was considered of limited clinical relevance, accepted only as supportive indicator to other (e.g. visual functional or steroid-sparing) outcomes
- vitreous haze has been accepted in an **acute setting** with a preference for a primary endpoint at 4 wks rather than the proposed 6 wks
- anterior chamber cells (5 unit scale) after 4 wks was not supported for moderate disease stages in a chronic setting, as not fully reflecting improvement (limited range of response)

Proposed label

For a **induction label** a feasible short time efficacy outcome should be planned

e.g. vitreous haze at 4 wks (but include supportive outcomes)

composite of needed **prednisone dose, AC and VH threshold values**

visual acuity might not be feasible for such short term outcomes

Maintenance labels will require long term efficacy

e.g for a planned label of both induction and maintenance, for suppression the proposed efficacy endpoint at 24 wks was considered much too long, for maintenance rather too short, moreover different inclusion criteria might be necessary.

Proposed label

It has to be specified, whether the drug aims at a **1st line or 2nd line** treatment. Currently for acute disease steroids are first line.

Specific forms of uveitis might be easier to address (homogeneous population)

Broad label claims can be supported, but

might be methodologically more challenging,

e.g. preferably exclude anterior uveitis in a trial (for methodological reasons)

Need for **clear definitions** of

- disease criteria

  study reading centers have been proposed to facilitate this
- etiology
- resistance to steroids

Other issues

Comparators:

- to position a drug on the market, an active comparator is preferred
- placebo might be acceptable for chronic quiescent disease

  e.g. a placebo comparator (sham injection) has been accepted for intermediate uveitis (slower disease progression), but not for anterior uveitis
- Placebo-add on to corticosteroid will raise less ethical concerns, but should reflect the later label claim

Concomitant therapies

Specific application systems

Specific dosage regimens

Conclusions

Rather heterogeneous proposals might be considered as valid, depending on exact disease definition and claim targeted

- acute – quiescent
- disease suppression – maintenance
- severe – moderate
- anterior / intermediate / posterior / panuveitis
- specific aetiologies (e.g. Behçet, autoimmune)
- age range

This has consequences with regard to endpoints, treatment duration, acceptable comparators/placebo, inclusion/exclusion criteria

There are no „one-fits-all“ solutions, many parameters have to be justified case by case

In practice MAA rather failed due to major design flaws or negative results (i.e. not effective or a non-sensitive endpoint has been chosen)