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EU Regulatory Workshop – Ophthalmology – Summary and Report

Clinical Development, Scientific Advice and Paediatric Investigation Plans

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Summary

The workshop aimed to share experience and get an update on existing and upcoming pharmacological treatments in eye disease. The focus was set on clinical development and methodological issues, including the choice of outcome measures, evolving towards a common understanding among regulators, academia and industry.

Visual Function Endpoints in Clinical Trials

Clinical Academic View: Eberhart Zrenner

Retinal structure and function is complex. Understanding of the disease, and the potential therapeutic mechanism is essential in order to target the appropriate endpoint. Patient reported outcomes are very important; as scored directly by patients, these are free of interpretation by the observer. Monitoring of visual function for safety and efficacy in very low and ultra-low vision patients is difficult; some of the on-going studies have developed novel tests in order to monitor ultra-low vision changes including activities of daily living, which, however, are not yet validated.

Industry View: Gabriela Burian

Different stakeholders have different expectations of what an endpoint can provide; satisfying all objectives in a single trial/ endpoint can be challenging. Evaluation of the treatment benefit overtime (mean average VA change), offers an overall more comprehensive assessment immediately after treatment initiation. Improvement in VA is the new aim particularly for macular diseases, but the relevant benefit that can be translated to the individual patient level needs to be established. Measurement of poor vision and vision in children remains a challenge. Open questions are the added value and clinical relevance of using co-endpoints with supportive surrogate markers, how best to demonstrate the correlation between function and anatomy, the use of other visual function assessments, and the future regulatory use for VF PROs?

Regulatory View: Jane Moseley

Demonstration of a clinically relevant benefit is essential in order to be able to make a judgment on risk and benefit; thus visual function endpoints are fundamental to the assessment of ophthalmological products. The limitations of conventional visual acuity assessments are understood. There is scope for widening and deepening the range of visual function and functional vision endpoints that can considered in the regulatory context that are of clinical relevance to the patient. Prospective

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discussions with regulators are possible, and welcome regarding (non-)product specific advice on qualification of surrogate endpoints and novel approaches.

Advanced Therapy in Retinal Disease

Regulatory View Committee for Advanced therapies: Lennart Åkerblom
Information was provided on the regulatory framework, consistency in production, biodistribution, specific challenges with ATMPS, proof of concept, tumourigenicity, risk-based approach, and combined ATMPs.

Regulatory View Committee for Orphan Medicinal Products: Stylianos Tsigkos
The Committee of orphan medicinal products acts as a gate opener for orphan products. Sponsors considering to apply are advised to start with a letter of intent to the orphan section of EMA and a subsequent presubmission meeting.

Clinical Academic View: Anthony Moore
Inherited retinal disorders represent a unmet need with no effective treatments. Advances in molecular genetics will lead to identification of causative genes; there is much to be learned about mechanisms of photoreceptor cell death, and multiple strategies of research are needed; patient selection is very important, and determining the treatment effect will be major challenge.

Industry View: Matthew Campbell, Paul Williamson
Advanced therapy products are complex with many challenges in the quality, nonclinical and clinical development. Examples are given. Early discussion with regulators is essential.

Macular Oedema

Clinical Academic View: José Cunha-Vaz
An overview of classification, frequency, characterisation, possible biomarkers, pathogenesis and treatment was given for macular oedema.

Industry View: Yehia Hashad
Regulatory guidance is sought on a range of issues: flexibility in the design of the clinical studies, target population definitions (baseline acuity, OCT types, duration of MO, sub-populations (e.g., focal vs. diffuse or ischemic vs. non ischemic), prior laser), optimum endpoints (as specific time points or mean change over time, reduction in treatment burden), calculation of non-inferiority margins, the role for laser or sham treatment as comparators, duration of trials, combination therapy, and addressing BRVO and CRVO as a single pivotal or separate studies.

Regulatory View: David Silverman
Factors dictating the expected duration of safety and efficacy data requirements are discussed including the existing knowledge and safety database with a product, the intended duration of treatment, unmet medical needs, the natural history of the disease, and formulation/implant release factors. If studies enrol both BRVO & CRVO patients, results for each condition need to be considered separately. The chosen primary endpoint needs to reflect clinically relevant effects of treatment; situations where mean BCVA at an single time-point, mean average and responder are useful are discussed. The choice of comparator varies with existence of licensed alternatives and disease related factors. Non-inferiority studies against a licensed alternative must demonstrate assay sensitivity, with the choice of the non-inferiority margin also considering the maximum difference between treatments that can be considered clinically irrelevant. Companies should consider how they will advise clinicians on concomitant use of their product with laser and how these data will be generated given the timing of combination and delayed effects on efficacy.

Dry Age-related Macular Degeneration

Clinical Academic View: Adnan Tufail
Dry AMD is a major public health issue because it is the most common cause of legal blindness in the developed world and will become more prevalent with the expected increase of population aged over 80 years of age. Moreover, no effective treatment is currently available for dry AMD. A very important issue is how to measure disease progression in clinical studies. The standard endpoint of high contrast visual acuity might be problematic: there are structural and functional markers. Colour Fundus Photos (CFP), OCT, low luminance visual acuity, reading speed, microperimetry, dark adaptation, contrast sensitivity and quality of life questionnaires, and their limitations are discussed.

Industry View: Oliver Zeitz
It could be argued that visual acuity is not the preferred outcome measure for clinical development in dry AMD. Morphological parameters have been developed recently and are under evaluation and could be utilised as outcome variables soon.

Regulatory View: Marco Coassin
No surrogate primary outcome for efficacy has yet been validated for this condition in a licensing procedure. Best corrected distance visual acuity may not be sensitive enough to assess disease progression within a reasonable time frame. Relevant secondary clinical/functional outcomes should be looked at closely in order to generate supportive evidence complementing the chosen primary endpoint. The clinical meaningfulness of the chosen endpoint should be justified. It might be possible to plan a trial with a suitable functional visual loss parameter as a primary outcome in an enriched population with greater risk of GA progression; implications for generalisabilty should be considered.

Uveitis

Clinical Academic View: Manfred Zierhut
Uveitis is a heterogeneous group of diseases making trials difficult. There is a need for better definition of entities and further validation of endpoints, and more randomised controlled trials with well-defined uveitis entities and specific endpoints dependent on aetiology. Longer follow up in studies is needed (recurrences: 1 year). Children with uveitis should also be involved in studies. Damage tends to develop with inflammatory activity; control of this inflammatory activity is the most important goal of treatment. Endpoints should reflect activity of inflammation as visual acuity is not always a good primary endpoint.

Industry View: Robert Kim
In developing trial designs for uveitis, heterogeneity in uveitis syndromes, the lack of accepted standard of care, and knowledge gaps in understanding the biology represent significant challenges.

Regulatory View: Karl-Heinz Huemer
Different trial design proposals might be considered as valid, depending on the exact disease definition and the claim targeted. This has consequences with regard to endpoints, treatment duration, acceptable controls, and inclusion/exclusion criteria. Many parameters could be justified case by case. Biomarker qualifications procedures are recommended for novel methodologies. Open questions for guidance include: managing standard of care including off label use, and absence of a uniformly accepted SoC, population definitions, appropriate steroid sparing endpoints, the choice of comparator, the most clinically relevant endpoints, the role of macular oedema as an endpoint, continuous or dichotomous data for the primary analysis, handling of combination treatments and rescued patients.

Ocular Surface Restoration

Clinical Academic View: Per Montan
Unmet needs in restoration of the ocular surface include the best topical steroid regime for low-risk corneal grafts, the add-on value of topical immuno-suppressants and/or anti-angiogenic treatments, the value of systemic immunosuppression and HLA-matching in high-risk grafting and allogeneic stem cell transplants, and the development of gold standard cultivation of (limbal stem cells) LSCs. Potential clinical trial design parameters, including endpoints for high-risk corneal grafting and LSCs are proposed.

Industry View: Giovanni Milazzo
Challenges for industry in the development of limbal stem cells are that the target disease is a rare condition, the severity grading of which is not established, that there is no suitable reference treatments, that the optimum approach to minimise the potential for bias remains to be established in addition to the most appropriate endpoint of efficacy.

Industry View: Claus Cursiefen
There is an unmet medical need with no specific licensed medical treatment for corneal neovascularisation (CNV), particularly in the context of corneal transplantation. It is proposed that inhibition of CNV is the most relevant primary endpoint to demonstrate efficacy of anti-angiogenic agents in patients with proliferative corneal new vessels uncontrolled under the current best available therapy and furthermore that this supports benefits for the patient in preventing the need for a corneal graft, as well as improving graft survival if transplantation becomes necessary.

Regulatory View: Gopalan Narayanan
Open questions for guidance: the best methods to assess severity of limbal stem cell deficiency, and corneal surface restoration, and the duration of long term follow up needed. Also, the acceptability of corneal neovascularisation as an endpoint for primary or secondary prevention of rejection in corneal grafting or for angioregression is not yet established. Formal submission of biomarker qualification advice or opinion is recommended for novel methods such as corneal neovascularisation as an endpoint in confirmatory trials for corneal graft rejection, or methods to assess severity of limbal stem cell deficiency.

Dry Eye Disease and Meibomian Gland Dysfunction

Clinical Academic View: David Sullivan, Kelly Nichols, Anthony Bron
In the development of treatments for dry eye disease (DED), the common signs and symptoms do not correlate. New diagnostic approaches and outcome measures reflective of the disease are needed. We need rigorous criteria for each phenotype of dry eye. We need validated questionnaires and measures to quantify severity. We need to optimise tissue sampling and to select biomarker technology and associate those with clinical tests. Better tests to evaluate and grade Meibomian gland dysfunction (MGD) are needed. In MGD, there is a high need for additional randomised, controlled, double-masked treatment trials with clearly defined objectives, relevant outcome measures based on pathophysiology, and refined inclusion & exclusion criteria. There is a need to further characterise the natural history of MGD and to gain further understanding of the association with dry eye disease. A development and validation of a symptom questionnaire specific to MGD would be welcomed.

Industry View: Auli Ropo
Dry Eye Disease (DED) is a heterogeneous condition and both diagnosis and endpoints for clinical trials are diverse. The Industry would welcome harmonisation of the diagnosis and measures / endpoints for clinical trials where possible. Since we currently are lacking those, the best approach for the industry would be to allow some flexibility in designing the protocols and endpoints. However, these endpoints should be very well justified and could be based on the mechanism of action of the study drug. The development and acceptability of reliable biomarkers would be helpful. The clinically relevant change of symptoms is not clear. Evaluating symptoms is difficult since variability can be high and repeatability is a problem. It is not clear what are the signs to be used as inclusion criteria and what is a clinically significant change. Development of new pharmaceutical therapies is hampered by the lack of objective tests for response outcomes.

Regulatory View: Kerstin Wickström
We need a better understanding of the relevance and usefulness of different outcome measures in DED and the strengths and weaknesses of the symptom scales and visual function quality of life questionnaires. The population to include in a clinical trial needs to be better defined taking the reasons for the dry eye into account. Tools for standardised grading and evaluation of signs and symptoms of MGD are not available we need to learn about the overlap in symptoms compared to tear deficient dry eye. There is a confusion regarding criteria for selecting patients, which outcome measures that are of relevance and whether these should be different in evaporative or tear deficient DED. Currently, regulators require a co-primary endpoint evaluating a sign and symptoms (or at least one of these with strong support of the other), but there is a problem correlating signs and symptoms. Since this confusion is evident in the industry as well as among regulators, a meeting with an expert group to discuss how to handle these issues until further research is available could be useful.

Paediatric Investigation Plans in Ophthalmology

Some experience has now been gained with Paediatric Investigation Plans for products in ophthalmology indications. This workshop aimed to bring together regulators, clinicians and industry to consider and examine priorities for unmet pharmacological needs in paediatric ophthalmology, and consider critical issues of clinical trial design and development in paediatric uveitis, other anterior segment disorders, glaucoma and retinopathy of prematurity.

Conclusions

Further consideration is being given to development of guidance applicable to products for treatment of dry eye disease, and for macular oedema. The Qualification Advice procedure is recommended for novel methodologies and endpoints in the areas of inherited retinal disorders, non-standard visual function endpoints, use of co-endpoints, uveitis, corneal neovasularisation/graft rejection, and dry AMD. It is intended to continue to engage with expert groups as needed.

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Introduction

Ophthalmology is an evolving area. Many products are in development, some in 'new' ophthalmological indications, i.e. indications where no satisfactory treatment options are available. Such indications are emerging, for example, in retinal degenerations including dry AMD as well as inherited retinal disorders, and Meibomian gland dysfunction, and are being targeted by pharmacological treatments, cell or gene therapy. Besides requiring complex clinical trials, in a number of these diseases, efficacy endpoints and trial design parameters are not yet established.

Objectives

The workshop aimed to share experience and get an update on existing and upcoming pharmacological treatments in eye disease. The focus was set on clinical development and methodological issues, including the choice of outcome measures, evolving towards a common understanding among regulators, academia and industry.

The workshop brought together over 200 attendees including regulators (clinical ophthalmology assessors from the national agencies, national experts, CHMP and SAWP members active in the area of ophthalmology) as well as clinical ophthalmologists and pharmaceutical industry representatives working in early to late development in ophthalmology. Health professional and patient representatives were also invited. We requested topics for discussion from stakeholders.

Report Day 1 Clinical Development, Scientific Advice

Visual function endpoints in clinical trials

Clinical Academic View: Eberhart Zrenner
Professor, Institute for Ophthalmic Research, Universität Tübingen

There are many possible visual endpoints that examine safety, and benefit; their reliability, and feasibility in terms of what patients can tolerate, and what is a proper target of functional testing have to be taken into account. The discussion featured an overview of retinal structure and function, the relationship between structure and function in addition to measures in psychophysics, electrophysics, imaging and the importance of assessing activities of daily living and assessing patient reported outcomes for visual function.

The overview of retinal structure and function underscores the complexity of the system and the need for understanding of the disease, and the potential therapeutic mechanism in order to be able to target the appropriate endpoint. For assessment of distance visual acuity, EDTRS is now standard; Freiburg visual acuity testing is also useful in assessing visual function in patients with low vision. This is semi-automated even down to hand movements and counting fingers, a numeric value can be assessed which correlated with EDTRS, and is not influenced by investigators.

Apart from clinical history and the standard clinical eye examination, additional assessments can include colour vision assessment, reading speed, dark adaptation, visual field, and electrophysiological assessments. Various options for colour vision testing (Lanthony Panel D-15 Test, Roth 28-hue Test, Farnsworth-Munsell 28 or 100 Test and Anomaloscopy), contrast sensitivity (Pelli-Robson Chart, Mesoptometer-With and without glare and Hamilton Veale Test) and visual field (static and kinetic) testing are available. Microperimetry may be helpful for example in central visual function assessments; for example in AMD, is the area of geographic atrophy increasing? Eye movement compensation is very valuable. The possibilities for dark adaptation (Adaptometer) and pupillometry (AMTECH Pupillograph) to aid understanding are highlighted.

For electrophysiology, the International Society of Clinical Electrophysiology of Vision (ISCEV) has determined the relevant standards and these are available on their website. Options include Electroretinogram (ERG), Visually evoked potential (VEP), Multifocal ERG (mfERG), Pattern ERG (PERG) and Electrooculogram (EOG). Specialised ERGs exists if necessary. ERG is not just the 5 basic responses (Isolated rod responses , Rod and cone Maximum Responses, Inner Retina Oscillatory Potentials, Isolated Cone Responses and Cone flicker Responses) but much more and the choice of test depends on understanding the putative action of a drug and exact question to be asked, in order to be able to select the correct test.

Imaging methods are also very useful including autoflourescence, and OCT, with Multimodal Mapping (Structure-function correlation) offering new perspectives. Patient Reported Outcomes are very important; as scored directly by patients, these are free of interpretation by the physician or observer, and should give an account of how the patient functions or feels relative to a health condition or therapy. Good measurements should have unidimensionality, hierarchical order, and equal interval spacing. A PRO would measure any of the following: Symptoms, Symptom impact and functioning, Disability or handicap, Adverse events, Treatment tolerability, Treatment satisfaction or Health-related quality of life. A number of instruments are available. (Activities of Daily Living Scale (ADVS)-*Reading, orientation/mobility, finding objects, social participation, financial handling….-,* Daily Living Tasks Dependent on Vision (DLTV), Impact of Vision Impairment (IVI), Macular Disease Quality of Life Questionnaire, NEI-VFQ 25 (most common, well-equipped), Visual Function Index (VF-14), Low-Luminance Questionnaire (LLQ), Miedziak's instrument, Vision-specific sickness impact profile (SIPV), Turano's instrument, Vision-Related Quality of Life Questionnaire, Retinopathy-Dependent QOL). An example is given of an on-going trial in legally blind patients where the primary outcome measures comprises daily living tasks, recognition tasks, mobility, or a combination thereof. Secondary outcome measures include visual acuity/light-perception and/or object-recognition, measured with tests such as Freiburg acuity, *BaLM ("Basic Light and Motion Test")*, BaGA (recognition of stripe pattern), VFQ-25, and patient long term safety.

Retinal structure and function is complex. Understanding of the disease, and the potential therapeutic mechanism is essential in order to target the appropriate endpoint. Patient reported outcomes are very important; as scored directly by patients, these are free of interpretation by the observer. Monitoring of visual function for safety and efficacy in very low and ultra-low vision patients is difficult; some of the ongoing studies have developed novel tests in order to monitor ultra-low vision changes including activities of daily living, which, however, are not yet validated.

Industry View: Gabriela Burian
Global Program Medical Director, Novartis

Historically, for industry, the focus has been on best corrected visual acuity as this is the tool which is most familiar, most engaged with, the most discussed and the basis of regulatory approvals. The talk summarises visual function benefit from different perspectives, specific analyses, historical and current status, future development and which endpoints would be relevant for all stake holders moving forward.

From the patients' perspective: the endpoint should be one that patients should be able to relate to; to show improvement in symptoms of visual function loss. The patient's interest is to maintain and/or regain quality of life dependent on visual functions, while under a medical or surgical treatment at individual patient level. From an industry perspective, an endpoint should be able, on average, in a broad population to quantify, evaluate and demonstrate efficacy in terms of affecting the symptoms of visual function loss. The endpoint should be able to demonstrate safety of the treatment compared to what is otherwise available. There is a need to demonstrate an overall favourable, positive benefit/risk profile of a treatment better than current therapy but also need to know that these endpoints are relevant and applicable to clinical practice. An endpoint is needed that facilitates access of patients/ clinical community to the treatment (market access, reimbursement) and delivers an impact on quality of life (health economics vs. comparator). In healthcare systems` perspective, the benefit of treatment vs. the burden of disease or treatment at individual/group patient level has to be considered. What is the impact on population health (population health economics, avoidance of associated concomitant diseases and healthcare burdens)? How do we go from visual function endpoint in studies- to health economics? This needs to be addressed at early phase before engaging with MAA at approval stage. It is challenging with many objectives in fewer trials.

Historically, in diseases of the macula, because of disease progression, efficacy outcomes primarily analysed the "*avoidance of VA loss" as the* proportion (%) of subjects with "loss of <15 letters"; no loss (i.e. ± 5 letters) was relevant and of clinical benefit to the patient. The outcome was evaluated at a pre-determined primary/secondary timepoint compared to baseline, i.e. 12/24 months vs. baseline. Based on what was known about macular disease, an average outcome of >50% patients avoiding loss was considered clinically relevant compared to no treatment. With major benefits in macular research, which appears like accelerated field, now avoidance of VA loss is no longer acceptable for patients or other stakeholders. Efficacy outcomes, primarily analysing the *"VA gain"*, through mean VA change or the proportion (%) of subjects with "gain >0, 5,10, 15 letters", VA gain has become the clinically relevant outcome.

How do we measure how much gain is clinically relevant? The predetermined timepoint of evaluation was month 12 compared to baseline. Difference in mean VA change between compared treatments on

average of 10-20 letters (2-4 lines) is considered as clinically meaningful difference that demonstrates efficacy. As a secondary endpoint, the proportion of patients with VA gain >10 letters, >15 letters (>2/3 lines) at month 12: >40% is also topical. Which is better for linking to the individual patient need - the mean change or the proportion? To further understand what is relevant to the patient, the efficacy should be assessed over the entire period. The average of each timepoint mean VA change " mean average VA change" evaluates the benefit outcome over the entire observation period taking account of the variability between visits, and the onset of benefit immediately after treatment initiation.

Industry is still at a loss how to measure poor vision as Standard ETDRS-like charts and BCVA protocols are not fully suitable for assessment of poor level VA, i.e. Count Fingers(CF), and Hand Motion (HM). Clinical and paraclinical methods are more useful but not standardised. A similar challenge exists in children who are not of reading age. Co-endpoints may be useful as primary endpoints with supportive surrogate markers are needed to better assess the overall benefit achieved in individual patients.

Open issues include questions such as: are predictive endpoints/biomarkers of disease progression/function loss valuable? The assessment of the histopathologic characteristics that cause the visual function loss as a "surrogate" marker of the functional loss and its characteristics. (i.e. describe type, predict the progression of function loss)? How best to demonstrate the correlation between function and anatomy? (VA vs. HD-OCT *or* microperimetry vs. HD-OCT), the use of Electroretinography (ERG), and microperimetry as options to assess physiopathology of visual function? The use of Adaptive Optics (AO) as an option to assess the rate of photoreceptor loss in conjunction with other tests? The clinical relevance and clinical applicability of other visual function assessments? The future use in demonstration of clinical relevance for the regulatory context with PROs such as National Eye Institute (NEI) standardised Visual Function Questionnaire (NEI VFQ-25) – a tool providing reproducible and valid data when used across multiple conditions of varying severity, where a gain of 10 or more letters has been shown to lead to an increase in the composite NEI-VFQ-25 scores by an amount judged to be clinically significant in diseases of the macula.

Different stakeholders have different expectations of what an endpoint can provide; satisfying all objectives in a single trial/ endpoint can be challenging. Evaluation of the treatment benefit overtime (mean average VA change), offers an overall more comprehensive assessment immediately after treatment initiation. Improvement in VA is the new aim particularly for macular diseases, but the relevant benefit that can be translated to the individual patient level needs to be established. Measurement of poor vision and vision in children remains a challenge. Open questions are the added value and clinical relevance of using co-endpoints with supportive surrogate markers, how best to demonstrate the correlation between function and anatomy, the use of other visual function assessments, and the future regulatory use for VF PROs?

Regulatory View: Jane Moseley
Scientific Administrator Scientific Advice working Party European Medicines Agency

The regulatory perspective on visual function endpoints, based upon previous regulatory experience with scientific advice, and centralised marketing authorisation procedures for ophthalmological products. This was considered on a background of globalisation and increasing needs to address health technology assessments and use of novel methods and biomarkers. There are no European guidelines dedicated to the development of ophthalmology products; some references are made in the rhino-conjunctivitis guideline. Never the less, general guidelines relating one pivotal study, small populations, adaptive designs, missing data, control groups, and general principles of clinical trials are important and need to be highlighted. Focussing on phase III confirmatory studies and endpoints, attention is drawn to important principles outlined in ICH E8 and 9; the primary endpoint should reflect clinically relevant and important treatment effects based on the primary objective of the study. The CHMP generally interprets this as measuring how a patient feels or functions. Secondary endpoints should also be seen to be supportive. Surrogate endpoints, if used, should be reliable predictors of clinical outcomes. In Alzheimer's disease, the concepts of symptomatic progression as opposed to disease modification are distinguished where in the latter the changes in the clinical outcome are supported by changes in a fully qualified pathological biomarker. It is useful to consider as a frame of reference, measurements assessing the organ structure, organ function in an experimental setting such as visual acuity, visual field, contrast sensitivity and colour vision, to integrated functional vision such as reading ability, orientation and mobility, and lastly and more complex still, measurements relating to vision related quality of life. (Colenbrander 2010).

CHMP Scientific advice is a voluntary non-binding procedure, based on the European network of experts/working parties and committees. CHMP advice has been given on approximately 100 ophthalmology products, a large proportion of which are rare diseases.

Visual fields have rarely been proposed as a primary or co-primary endpoint, although this has been accepted as such in particular contexts with caveats such as the need to be supported by data such as test/retest reliability, sensitivity, and feasibility in the actual patient group, the definition of responders, and progression rate / linearity and information to support the clinical relevance of possible effect sizes.

When considering primary endpoints, the emphasis is frequently on visual acuity and on clinical relevance, and that *the quantification of the primary endpoint will need to be translated into clinical benefit.* For best-corrected visual acuity (BCVA) as a primary endpoint, EU regulators have variably commented in different contexts; - *the percentage of patients who gained more than 15 letters of best-corrected ETDRS visual acuity (BCVA) from baseline to 12 months is acceptable. - Additional efficacy analyses, allowing for repeated measurements over time, up to 12 months should be provided, assessing the sustained effect on change on BCVA over time. - It is essential that a clinically relevant treatment effect is also prespecified and 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. -The minimally clinically relevant improvement (perceived as such by patients) in this disease is around 10 letters. The improvement of at least 15 letters (responders) should be a key secondary endpoint.* EU regulators have also accepted mean change in visual acuity, however, secondary responder analyses have been considered helpful. Indeed *Visual acuity scores determined at one single time-point might be questionable, and a "mean VA score" over a longer period of time for example the last six months before study end may be more appropriate in certain contexts.* In the setting of non-inferiority studies, a single time point was preferred over mean average over multiple time points to allow better discrimination between treatments.

The correct handling of missing data is essential; it is important that approaches taken are conservative, allow sensitivity analysis, are pre-planned and that trials are designed in such a way as to minimise the impact of missing data. Findings should be robust to different approaches, particularly when there are extensive missing data and rescue treatments. The European guideline on missing data is recommended.

Patients with very low vision: Limited numbers of development programs with such populations have been presented for scientific advice. Possible approaches include: Attributing scores to semi-quantitative acuity in patients with very poor vision, Using best recovery of visual acuity per eye over baseline, Using best visual acuity per patient vs. baseline; Enrolling the better eye, or both eyes (as a Cluster or Average).

In the context of attributing scores to semi-quantitative acuity, i*t is essential that the study is controlled, and masking is strictly maintained, the rationale for the difference between categories would need to be justified at the time of submission including a full literature review demonstrating that the numbers proposed above are indicative of current clinical thinking: The allocation of "light perception" category to the scale at all requires particular justification. Consider a "worst case" evaluation, overemphasis of improvements at the lower end of the scale should be avoided, a range of sensitivity analyses should be provided using different values for the categories. The main difficulty will be defining what constitutes a clinically relevant difference with the proposed scale. Some form of responder analysis (with an clinically relevant definition of 'responder') would be of help. Clinical global impression (CGI), could well be of importance (again provided that there is certainty on the blinding) to demonstrate that the magnitude of the statistical significance does not depend on the numerical values assigned.*

Licensing experience and visual function outcomes; A list of European centralised licensing procedures for ophthalmological products is presented; the overall success rate for ophthalmology products is approximately 70% and is comparable to other published data on overall rates of success. The centralised procedure provides a simultaneous marketing authorisation in all 27 European Member states. Other EU licensing procedures (mutual recognition, decentralised or National licensing procedure) are not considered in this analysis. Based on the Centralised licensing experience for ophthalmological products- examples of major objections raised during the marketing authorisation procedure in relation to visual function endpoints are provided: The foremost issue is the demonstration of clinical relevance. Amongst examples examined was a change to the primary endpoint after the study start. This is a particularly high risk strategy and would be actively

discouraged. Additional issues related to the strength and consistency of evidence provided in relation to efficacy and safety.

Examples of Other Concerns relating to visual endpoints were *floor effects, the absence of other tests of visual function (such as contrast sensitivity, visual fields, automatic perimetry, ERG), the distinction between patients where the active disease was in the eye with the best visual acuity or the eye with the poorest visual acuity (patients with active disease in their best eye actively learn to compensate by developing extrafoveal fixation and improved abilities to scan their defective visual field over a visual target), the need for patients' evaluation of subjective qualities of vision that are difficult or impossible to assess qualitatively (such as metamorphopsia, relative central scotoma, binocular function, etc), the use of LOCF, the validation status of the various scales used in the studies, the provision of Health-related quality of life (HQL) results, the provision of plots (with confidence intervals) of visual acuity over time from pivotal clinical studies, and absence of re-estimation of sample size/power calculations.*

Health technology assessment
A significant challenge today is that all new medicines are not potentially accessible by all patients in need, and at there are diverging development requirements for the Reimbursement/ health technology assessment perspective and the Licensing viewpoint. The EMA has a pilot process for multi-stakeholder involvement in early-stage drug development to improve clarity, provide input and alignment among the stakeholders regarding what constitutes a medicine's value and the evidence required to demonstrate that value most effectively.

EMA FDA parallel advice
Another parallel Agency procedure provides for increased dialogue between Agencies and sponsors from early stages of development with the aim to exchange views, share expertise, optimise and facilitate global development, whilst meeting both agencies' requirements.

Biomarkers: There are 2 new regulatory procedures focused on the qualification of novel methodologies or biomarkers. A *CHMP Qualification Advice provides input* on future protocols and methods for further method development aiming towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted (confidential). A *CHMP Qualification Opinion* pronounces on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a R&D context (non-clinical or clinical), based on the assessment of data, which is not product-specific and involves a qualification team, peer review, public consultation, and is ultimately published.

Demonstration of a clinically relevant benefit is essential in order to be able to make a judgment on risk and benefit; thus visual function endpoints are fundamental to the assessment of ophthalmological products. The limitations of conventional visual acuity assessments are understood. There is scope for widening and deepening the range of visual function and functional vision endpoints that can considered in the regulatory context that are of clinical relevance to the patient. Prospective discussions with regulators are possible, and welcome regarding (non-)product specific advice on qualification of surrogate endpoints and novel approaches.

Advanced Therapy in Retinal Disease

Regulatory View Committee for Advanced therapies: Lennart Åkerblom
Member Committee for Advanced Therapies, Swedish Medicines Agency

Regulatory framework for ATMPs
Annex I of Directive 2001/83/EC, revised through directive 2009/120/EC, introduces new definitions for somatic cell therapy and gene therapy Medicinal products. Also, the technical requirements are updated. The basic requirements for tissues and cells are outlined in Directive 2004/23/EC and its technical directives. Specific guidelines as well as general information for cell and gene therapy products can be found on EMAs website. There are three types of products defined within the regulation of ATMPs. Cell and gene therapy products have been regulated since 2003. Tissue engineered products were introduced into the legislation by the Regulation of ATMPs. The Regulation on Advanced Therapies (1394/2007/EC) introduces the certification procedure for Quality and Non-clinical data. With this Regulation follows also some incentives for SMEs, e.g. 90 % reduction on scientific advice fee. Furthermore, it is also possible to have the product classified whether or not it is an ATMP.

Consistency in production

The main objective should be to document the quality profile and consistency of both the product and the production process, using generated data and supportive data to justify the development strategy and the current set of specifications proposed including control of the process and stability data. The cellular starting materials should comply with the requirements of Dir. 2004/23/EC and the corresponding technical directives. The manufacturing process should be validated to ensure product consistency. Also, the manufacturing process should comply with the technical requirements defined in dir. 2009120/EC. The manufacture of drug substance and drug product is performed in compliance with GMP requirements. The Control strategy for the manufacturing process for the drug substance and the drug product is mainly based on characterisation data.

Characterisation studies should involve methods that would be suitable to ensure consistency of the product. A validated potency assay based on the functional properties or mode of action of the product should be introduced. The product characterisation should provide information on critical parameters of the cells or the product. The tools for in–process controls and release and stability testing have to be qualified. Specific limits need to be defined and set for composition, dose and level of impurities. If changes are introduced in the manufacturing process during or after the pivotal clinical studies, comparability of the product before and after the change(s) has to be demonstrated. A draft guideline on changes during development of GTMPs has been elaborated. The consequences of changes introduced during development in terms of regulatory compliance may be complicated. An evaluation of the impact such changes might have on the safety and efficacy is therefore needed.

Potency of ATMPs
Bioassays measure potency by evaluating a product's active ingredients within a living biological system. Bioassays can include in vivo animal studies or cell culture systems and should reflect the relevant biological attributes that are identified during development. Analytical assays can provide extensive product characterisation data by evaluating molecular attributes of the product. These attributes may be used to demonstrate potency if the surrogate measurement(s) can be substantiated by correlation to a relevant product-specific biological activity. Clinical study results may be correlated to product´s potency. Therefore, clinical study results may be used to establish a correlation between the product´s clinical efficacy and a potency measurement.

Biodistribution
Biodistribution is a complex issue that relates to cell localisation and migration as well as survival and differentiation status. The design of biodistribution studies conducted in animals must include a consideration of multiple factors: The methods applied to cellular detection and their sensitivity. Is single species adequate? Will xenogenic cells (i.e. human cells) migrate in a relevant way in an animal model? Can a homologous model be used? What is the route of administration? There is no single satisfactory method of tracking the fate of cells in vivo. It may be done through the use of reporter probes imaging. Cellular markers of phenotypic differentiation, and genetically modified tagging of cells may allow the monitoring of CBMPs – methods to address the safety concerns related to biodistribution.

Specific challenges with ATMPs
The need for biodistribution data will depend on the clinical evidence available. Since adequate cell tracing is often difficult in humans, non-clinical data may become necessary in a suitable animal model. When a well-developed animal model is available, evidence for robust proof-of-concept preclinical test results is valuable and informative. Tumourigenicity studies are considered essential for products in which a tumourigenic potential of the cells cannot be ruled out, e.g. regarding self-renewal of undifferentiated cells. Ectopic tissues formation and migration from the site of transplantation are also concerns. Control of cell differentiation should be highlighted. Clinical considerations in the establishment of the optimal effective dose should be addressed. The risk of transmission of infectious agents should also be investigated (e.g. use of material of animal origin).

There are several specific challenges with ATMPs as possibilities of masking and the feasibility of dose finding and biodistribution studies in humans.

Risk-based approach
The draft guideline presents the methodology of the risk-based approach and is intended to support the Applicant to identify the risks and associated risk factors, and to establish a risk profile of their ATMP under development. With the use of the identified risk profile the Applicant will be able to justify the extent of data to be included in the MAA dossier. The guidance does not provide a rigid classification system of different risks and it should therefore be distinguished from Benefit/ Risk Assessment and Risk Management in the context of a marketing authorization application.

Combined ATMPs
Combined ATMPs means that they incorporate as an integral part of the product, one or more medical devices or one or more active implantable medical devices. Also, its cellular or tissue part must contain viable cells or tissues or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to. If the Medical Device is already CE marked, Does the ATMPs incorporate as an integral part this MD? Where the medical device or active implantable medical device is combined with the cells at the time of the manufacture or administration of the finished products, they shall be considered as an integral part of the finished product. If the product contains a structural component that is not CE marked? The structural component can be an integral part of the finished product. It can also be considered as a support to contain or preserve biological characteristics and functional activities of the cells. The structural component should be inert.

Information was provided on the regulatory framework, consistency in production, biodistribution, specific challenges with ATMPS, proof of concept, tumourigenicity, risk-based approach, and combined ATMPs

Regulatory View Committee for Orphan Medicinal Products: Stylianos Tsigkos
Scientific Administrator, Committee for Orphan Medicinal Products
The orphan framework has been put in place to provide incentives for the development and marketing of medicines intended for diagnosis, prevention or treatment of unprofitable medical conditions, such as rare diseases. Criteria for orphan designation are defined in Regulation (EC)141/2000 and can be generally listed as: rarity/insufficient return of investment, severity of the target condition, significant benefit over satisfactory treatments (as well as the implicit criterion of medical plausibility).

There is an orphan designation/ authorisation gap that can be identified for ophthalmology: at the time of the ophthalmology workshop, no marketing authorisations for orphan medicinal products for eye disorders were granted, but 40 orphan designations have already been granted. Retinitis pigmentosa is the most frequently designated target condition.

Examples of the criteria for designation can be found in the following case studies:
1) An overview of the products designated for the treatment of RP reveals that most sponsors (6/8) presented preclinical data in relevant preclinical models to justify medical plausibility.
2) An overview of the products designated for the treatment of Uveitis revealed that with regards to significant benefit, most sponsors justified significant benefit on the grounds of a clinically relevant advantage, and in particular with regards to a potential for improved efficacy over authorised counterparts. The fulfilment of significant benefit has to be reviewed at the Marketing authorisation stage. With regard to withdrawals during the evaluation stage, the applicants were considerably more successful compared to overall orphan procedures.

The Committee of orphan medicinal products acts as a gate opener for orphan products. Sponsors considering to apply are advised to start with a letter of intent to the orphan section of EMA and a subsequent presubmission meeting.

Clinical Academic View: Anthony Moore,
Honorary Consultant Moorfields Eye Hospital, Institute of Ophthalmology, UK
Professor Moore discussed the diagnosis of inherited retinal disorders, the molecular genetics, current treatments, strategies for developing new treatments, and assessment of treatment effects. There are many genetic retinal disorders; as a group, it is the 2nd commonest cause of childhood blindness, and tends to affect adults of working age affecting 1/4000 of the population; 50% of cases have no family history. There are no available medicinal therapies.

These diseases are classified as diseases confined to eye- or associated with other systemic disorders. They can be stationary or progressive, and can also be classified by mode of inheritance, and site of dysfunction. Most progressive dystrophies affect both classes of photoreceptors; patients are interested in preservation of cone function which is the challenge for treatment. Classification is increasingly being based on molecular diagnosis. Phenotypes can vary. There have been major advances in molecular genetics which together with the phenotype, will identify subtypes. The identification of genes helps with molecular diagnosis, improves genetic counselling, helps understand disease mechanisms, and improves prospects for treatment; either gene specific or generic such as based on growth factors. Knowing genotypes allows better evaluation and ability to stratify trials of treatment. There is much genetic heterogeneity. An interaction of rods with cones has also been identified for diseases with rod only genes affected. Many affected genes are not eye specific but because of high metabolic activity in eyes, this may lead to disease manifestation in eyes only.

Characterising retinal disorders also requires identifying the cells affected, and the pattern of disease on electrophysiology, imaging and psychophysical testing. Judicious care is needed in selecting endpoints. Children present specific problems in this regard because, in many orphan retinal diseases, it is expected that treatment will work best early in disease, and therefore there is a need to test children and develop endpoints for use in children. This is an important area for development. The objective, if baseline vision is low, depends on whether the aim is to increase baseline vision or slow deterioration. Autofluorescence is mooted: can this be used to track cell death and to look at treatment response? Adaptive optics is suggested as a possible way of selecting patients for treatment trials, e.g. cone function in choosing those with structurally normal retinas, or for assessment of treatment effects. There are new possibilities opening up for looking at effectiveness of treatments.

Is abnormal function due to cell death or dysfunction; if cells are dead, treatment strategies are different. Are the photoreceptors salvageable; not imaging alone but also psychophysics may be needed for assessment. The hyper-fluorescent ring is proposed as a possible marker for residual outer segments; it is possible to plot the time course of shrinkage of the ring. Can this be an early surrogate marker for slowing degeneration? The challenge is to choose endpoints in clinical trials that tell us about slowing degeneration in visual acuity or visual fields. Surrogate markers are needed for early treatment effects. There is a need to be more imaginative and move away from visual acuity.

Inherited retinal disorders represent a major challenge with no effective treatments. The approaches to therapy depend on the disease and state of patients with the disease. With still healthy retina, and viable photoreceptors, gene replacement therapy is seen as a development option in addition to other strategies to protect photoreceptors (growth factors/ inhibition of apoptosis/ pharmacological agents). At the point of extreme photoreceptor loss, these strategies will not work, and there is a need for tissue replacement stem cell therapy such as, retinal or RPE replacement, or use of an artificial retina. There are a number of gene therapy trials on-going.

Inherited retinal disorders represent a major challenge with yet no effective treatments. Advances in molecular genetics will lead to identification of causative genes; there is much to be learned about mechanisms of photoreceptor cell death, and multiple strategies of research are needed; patient selection is very important, and determining the treatment effect will be major challenge.

Industry View: Matthew Campbell
Ocular Genetics Unit, Trinity College Dublin, Ireland
Retinitis Pigmentosa is genetically very heterogeneous- it is a major challenge to develop therapies to replace each identified gene abnormality, with currently 202 loci for 161 genes. AMD is also very heterogeneous involving multifactorial genetic variants in complement components. A challenge is to develop, using gene therapy, ways to facilitate drug delivery to retina to cross the blood retinal barrier. Further challenges involve translating the proof of concept in animals to humans and identifying appropriate endpoints in different clinical phases, and the duration of such trials.

Industry View: Paul Williamson
The Stem Cell Organization of J&J Biotechnology
Many complex aspects of stem cells have to be described and considered in terms of development:

- whether they are autologous, allogeneic or xenogeneic,
- the capacity of cells to differentiate (omnipotent to unipotent),
- the types of therapies, from somatic cell therapy, tissue engineered or combined with device where cells/tissues provide the primary mode of action, and
- the mechanism of action (trophic- with secretion of factors to support or repair injured tissues or preserve cells, or - regenerative; where cells are differentiated into an organ or organ system replace injured tissues and restores native function).

Safety issues of cellular biodistribution have to be considered.

For retinal disease, advanced therapies may satisfy unmet medical needs. Targeted therapies may offer advantages over systemic therapies. The subretinal space provides a site of immune privilege for allogeneic products. Retinal imaging is a rapidly growing field with opportunity for biomarker development. Targeted delivery however may not be satisfied by conventional surgery, resulting in a need for development of new surgical instruments, techniques and training. Current activity in allogeneic and autologous programs is increasing for ocular disorders. The work-stream is very different to conventional development programs for clinical trial supplies. In stem cell manufacturer, the first step in cell processing, of utmost importance, is the assessment of donor eligibility, and viral testing to ensure the reduction of the risk of transmission of infectious diseases; comprehensive

screening, eligibility assessment, traceability and testing are obligatory and critical for investigations of any suspicions of transmission.

Among the many challenges in the development of advanced therapy products for retinal disorders are firstly understanding the science including the availability of predicative animal models (e.g. absence of a macula, or the administration of human cells into other species adds other complications (xenograft) and which may not reflect the action in man, and addressing the risk of tumourogenicity such as differentiated products without 100% purity).

Challenges in quality development are: managing donor testing and eligibility, use of methodologies which require time and product-consuming test methods (e.g., sterility testing), a necessity to release product under restrictions (tests may not have been completed prior to administration to patient), use of aseptic, rather than sterile, investigative products, the management of comparability (for example if cells are derived from 2 different donors- are these comparable, possibly based on cell surface markers or are additional clinical trials warranted), characterisation- and achieving the ability to scale manufacturing to meet needs of the market.

Clinical challenges include dose development, since traditional PK does not apply and cyto-kinetics may be incomplete. Immunogenicity always needs to be addressed. For endpoints, the context is extremely important. Different endpoints must be sequenced through safety, proof of concept and dose finding to confirmation of a clinically meaningful benefit. Communication with regulators in needed. The choice of control is also an issue to be considered carefully, since sham surgical procedures may not be acceptable. Biomarkers and response instruments need to be considered. Other aspects which need to be addressed are retreatment and long term follow up.

Global development is a challenge. The definition and regulation of combination products differ world-wide. There is uncertainty and limited regulatory experience. This mandates early discussion with regulators. Paediatric regulations also need to be addressed including waivers. Reimbursements should be planned for.

Advanced therapy products are complex with many challenges in the quality, nonclinical and clinical development. Examples are given. Early discussion with regulators is essential.

Macular Oedema

Clinical Academic View: José Cunha-Vaz
Chairman, Department of Ophthalmology, Coimbra University Hospital, Portugal

Classification
Macular oedema is a non-specific sign of ocular disease occurring in a variety of situations with disruption of the blood-retinal barrier. Evaluation of clinically significant macular oedema affecting the vision, based on subjective measurement of proximity of oedema to the fovea, is being replaced by objective measurements such as optical coherence tomography (OCT) which can provide information on the amount and location of oedema and the presence of vitreoretinal interface abnormalities, and fundus photography to chart hard exudates.

Frequency
Diabetic retinopathy (DR) is a major cause of blindness and the primary cause of blindness in working-age individuals in developed countries. Diabetic macular oedema (DMO) is a common manifestation of DR, and is the main cause of visual impairment in patients with Type 2 diabetes. Although DMO does not cause total blindness, it frequently leads to a severe loss of central vision. The prevalence of diabetes is increasing dramatically and the burden of DMO is likely to increase as a result. Macular oedema occurs at a rate of 5 to 15% in the year following a branch retinal vein occlusion (BRVO). Some cases may improve spontaneously after occlusion, but this is not the case in central retinal vein occlusion (CRVO).

Characterisation
DMO can be seen as a complication of non-proliferative diabetic retinopathy (NPDR), along with progression to proliferative retinopathy. It appears as retinal thickening due to accumulation of fluid and is characterised on fundus photography by accumulation of hard exudates and microaneurysms in central 1000 microns. There appears to be a different evolution in different patients with similar metabolic control and duration of disease; not all patients develop persistent macular oedema, or

neovascularisation. Some patients may have a very slow progression of NPDR, while others may progress more rapidly, either with haemodynamic or thrombotic changes predominating.

Biomarkers
microaneurysm turnover may be used as a marker of microvascular disease activity to evaluate progression of NPDR by counting microaneurysms in sequential visits and identifying their exact location in the retina. This allows identification of new microaneursyms (marker of increased disease activity and leakage), and disappearance of microaneurysms (due to capillary closure). Patients with higher microaneurysm turnover have been shown to be more likely to develop DMO. Other markers of DMO are retinal thickness as measured by OCT and visual acuity.

Pathogenesis
DMO is caused by a breakdown in the blood-retinal barrier, due in diabetes to multifactorial changes initially in the inner blood-retinal barrier, and in vein occlusion to haemodynamic changes. Inflammation then leads to changes in the outer blood-retinal barrier. VEGF seems to play a major role in the pathogenesis of proliferative DR and DMO. Since the pathogenic profile varies among patients, personalised strategies are required to manage the disease effectively.

Treatment
In DMO, systemic treatments play an important role, and include metabolic control, management of blood pressure and lipid lowering. Local treatments include laser, intravitreal antiangiogenics and steroids, and vitrectomy. Laser is typically used in cases either with no central involvement or not causing visual impairment, whilst anti-VEGF monotherapy is becoming the choice for DMO with central involvement and vision loss, with steroid therapy an option for persistent cases. The response to anti-VEGF treatment varies, and some patients may show little or no response. In retinal vein occlusions intravitreal steroids and anti-VEGF therapy are used in cases of macular perfusion and macular ischaemia, with laser of use in situations of neovascularisation. Response to treatment may be measured by improvement of visual acuity (as a measure of photoreceptor status) and retinal thickness (as a measure of leakage).

An overview of classification, frequency, characterisation, possible biomarkers, pathogenesis and treatment was given for macular oedema.

Industry View: Yehia Hashad
VP, Clinical Development, Therapeutic Area Head Retina, Allergan
Until recently the standard of care in DMO was laser photocoagulation which slows progression of vision loss; however, with this treatment vision improvement is uncommon. Ranibizumab (Lucentis), recently approved in Europe to treat patients with vision impairment secondary to DMO, has been shown to improve vision. Data have recently been published showing the effects of other anti-VEGF therapies and steroids on DMO. In retinal vein occlusion Ozurdex and Lucentis have recently been approved for the treatment of macular oedema secondary to BRVO and CRVO.

Recent clinical studies in DMO and RVO populations show a variety of inclusion and exclusion criteria, particularly in regard to baseline visual acuity, OCT findings, HbA1C, and duration of macular oedema. Some flexibility in the design of the clinical studies will accommodate new advances in technology and will facilitate recruitment in future studies. However, such variations in target populations may limit comparisons of results across trials. Baseline visual acuity differs across studies (potentially impacting study results), OCT instrumentation types are different and consequently measurements of thickness may vary. Duration of macular oedema prior to enrolment could affect the study results, and use of different definitions in certain sub-populations (e.g., focal vs. diffuse oedema or definition of ischemic vs. non ischemic cases) could lead to different results. Finally the proportion of patients with prior laser treatment varies across studies.

A range of different endpoints have been used in recent studies in DMO and RVO. While some endpoints are evaluated at specific time points others represent a mean change over time. Assessment of efficacy based on the mean change in a variable over time (area under the curve approach) takes into consideration multiple treatment effects and longer durations of treatment and is an accepted technique in other therapy areas, though consideration must be given to what would be a clinically meaningful value using such a technique, and AUC may differ if measured over different time periods. Reduction in treatment burden is also being considered as an endpoint for new therapies which are shown to be non-inferior to the current standard of care with regard to efficacy and safety. A further area for discussion is the calculation of non-inferiority margins.

Sham treatment and laser have been used as comparators in studies in DMO and RVO. In light of recent data that have shown superior effects of pharmacologic treatment over laser there is need for guidance over whether there is still a role for laser or sham treatment as comparators in future pivotal trials.

The duration of clinical trials in DMO has also varied across different development programs, though in RVO, trials with assessment of efficacy at 6 months and a further 6 months of safety data have been acceptable. In DMO, it is unclear whether the timepoint for assessment of the primary endpoint is dependent on the novelty of the product, the nature and therapeutic class of the product, whether the product is already licensed in other indications, or the expected frequency of treatment.

Regulatory guidance is also sought on the combination of two pharmacologic agents versus a combination of pharmacologic agent and a procedure (e.g., laser), and the duration of follow-up for such combination studies, and the acceptability of inclusion of BRVO and CRVO patients in a single pivotal study for a new RVO therapy, as opposed to separate studies for each sub-indication.

Regulatory guidance is sought on a range of issues: flexibility in the design of the clinical studies, target population definitions (baseline acuity, OCT types, duration of MO, sub-populations (e.g., focal vs. diffuse or ischemic vs. non ischemic), prior laser), optimum endpoints (as specific time points or mean change over time, reduction in treatment burden), calculation of non-inferiority margins, the role for laser or sham treatment as comparators, duration of trials, combination therapy, and addressing BRVO and CRVO as a single pivotal or separate studies.

Regulatory View: David Silverman
Clinical Assessor, UK Medicines and Healthcare Products Regulatory Agency

The duration of clinical studies in DMO and RVO should reflect the length of time required to demonstrate a sustained effect on the chosen endpoint, though the existing knowledge of the duration of action of a particular class of drug should also be considered. There is also a requirement for long term safety data, particularly for drugs intended for long-term treatment in chronic diseases. While consideration should be given to the presence of an existing safety database in an alternative population, safety data from use in one population (e.g., AMD) may be not attributable to another population (e.g, DMO, which affects a younger population, more prone to infections, and at increased cardiovascular risk). In a variation to an existing license for a new indication, a single pivotal study is in principle acceptable if it provides compelling evidence of efficacy (both statistically and clinically). This is further detailed in EMA guidance document CPMP/EWP/2330/99.

In general, 1 year efficacy and safety data from 2 studies are expected prior to approval. However, consideration is given to the current level of knowledge for sustained effects of treatment with different classes of drug. If efficacy has not been robustly demonstrated to support the recommended posology, additional data may be requested. The presence of existing licensed therapies may also affect required study duration – e.g., in an area of significant unmet medical need, a trial showing superiority over control may be shorter than a non-inferiority study of a new product against a comparator in the same class.

In DMO recent data have demonstrated the sustained effect of VEGF inhibition over 2 years (DRCR.net and READ-2 studies). This means that in theory 1 year data could be acceptable for VEGF inhibitors in DMO. Previous studies in DMO have used laser as a comparator, the effects of which are not apparent at 1 year, so longer term efficacy data have been required to demonstrate superiority. A 1 year study comparing a new product against a VEGF inhibitor may have a primary endpoint at one year, with extended follow-up to clarify long-term posology and use with laser.

Whilst RVO could be considered a one-off insult, as opposed to the on-going insult and chronicity of DMO, a primary endpoint at 6 months is unlikely to be acceptable in future applications, especially since in BRVO, some patients with macular oedema can be expected to improve spontaneously by 1 year. 2 year follow-up of neovascular complications and long term effects on retinal ischaemia are also expected, potentially as a post-approval commitment.

In the case of sustained release formulations or implants, the length of follow-up will depend on the duration of action of the product. There is a requirement to not only demonstrate a sustained effect over the life of a single implant but also to show safety and efficacy after retreatment and to provide guidance on retreatment schedule. In both RVO and DMO companies are encouraged to consider investigating flexible dosing regimes (perhaps after an initial fixed regime). However it should be recognised that this complicates the statistical interpretation of efficacy data, and so flexible treatment

criteria should be strictly pre-defined. Companies could also consider using a re-randomisation schedule (eg, in the second year of a 2 year study).

The confirmatory trial population should generally be reasonably heterogeneous and should mirror target population. A single trial could be acceptable if large enough, and able to demonstrate clear efficacy with no safety concerns. If studies enrol both BRVO & CRVO patients, results for each condition need to be considered separately. If separate studies are conducted for BRVO and CRVO patients and one trial is negative, a submission in other type would be possible, but would be regarded as a single pivotal study. An attempt should be made to include patients with ischaemic RVO; the absence of these patients could lead to restricted indication, and potentially a request for follow-up studies. The efficacy of some products for macular oedema varies with the duration of the disease, so patients with a range of disease durations should be included where possible.

The chosen primary endpoint needs to reflect clinically relevant effect of treatment, and the results will be reviewed in the context of the overall findings of the clinical package. The proportion gaining 15 letters is a well-established and clinically relevant endpoint, however, as a responder analysis there is some loss of information from an otherwise continuous variable. If not primary, it should be considered as a key secondary endpoint. The mean change in BCVA is also well-established and clinically relevant, though fluctuations in visual acuity can make BCVA an imprecise variable, and measurement of BCVA at a single endpoint can miss important treatment differences occurring during the course of the study. Mean average change in BCVA is becoming a more frequent endpoint; it minimises the effects of variability in VA during the study, potentially reducing number of subjects required, and is more suitable for longer studies, though it may be less conservative than mean change in BCVA in non-inferiority studies due to lower variability, and thus is less suitable in this setting.

Each of these primary endpoints answers a slightly different question, and each may be acceptable, but should be adequately justified taking into account other factors such as the natural course of the disease, and the population etc. The overall findings of data will be considered.

Secondary endpoints could include change in macular thickness, categorised change in BCVA, development of neovascularisation (in RVO), need for rescue therapy, progression or development of retinal ischaemia (in RVO), and a quality of life measure.

With regard to choice of comparator, when no licensed alternative exists, a superiority trial against placebo is standard. In RVO and DMO, licensed treatments now exist, and it may prove difficult to recruit subjects to trials if there is a chance they may not receive active treatment. The trend now is for non-inferiority studies against a licensed alternative. The regulatory concern with this approach is firstly the lack of assay sensitivity, and secondly the difficulty in interpreting safety findings in absence of a placebo group. An acceptable non-inferiority margin needs to be chosen, taking into account not only the magnitude of the effect size of the control over placebo, but also the maximum difference between treatments that can be considered clinically irrelevant. Non-inferiority margins involving visual acuity should generally be conservative due to the variability and subjectivity of this endpoint. The lack of safety data from untreated subjects in non-inferiority studies means that additional safety data may be requested if potential signals are observed.

Although therapies have recently been approved for DMO and RVO, little is known about their long term effectiveness, whilst laser has proven effective at limiting vision loss over long term in both conditions. Companies should consider how they will advise clinicians on concomitant use of their product with laser. This information could come from use of laser treatment in planned studies, e.g. as an adjunctive treatment. Since the effects of laser are delayed, participants should be followed for a sufficient period to account for these delayed effects.

Combination therapies are generally employed either to improve the benefit-risk profile through addition or potentiation of individual therapeutic effects, to counteract an adverse effect of one product, or to simplify therapy by reducing the number of doses required. There is a rationale for combining medicinal products with procedures such as laser, since the mode of action is complementary. However, the duration of action is likely to be significantly different, with the effects of laser not immediately apparent after treatment. The length of follow-up therefore needs to account for the delayed effects of laser, and a primary endpoint at year 1 is unlikely to be considered acceptable. The timing of laser treatments is an area for further discussion. Previous studies have involved administration of laser from 30 minutes to 24 weeks after a VEGF inhibitor. It is plausible that waiting for the retinal oedema to resolve after administration of a medicinal treatment may increase the effectiveness of laser therapy.

Regarding the need for development of treatments, particularly in DMO, to prevent loss of visual acuity, the main issue foreseen would be the appropriate length of follow-up to capture a treatment effect, such as the reduction in the risk of visual loss.

On the suitability of microaneurysm turnover as a primary endpoint in studies in diabetic retinopathy, its relationship to visual acuity is not clear and so it would be more suitable as an associate endpoint where a claim of treatment or prevention of vision loss is sought.

In terms of the practicality of recruiting subjects with a range of disease durations in MO, where possible, patients with more chronic disease should be included, to investigate whether products are equally effective in patients with chronic and recent disease. The determination of disease duration is not straightforward though, since patients may not initially lose visual acuity and may go undiagnosed for some time prior to presentation.

Factors dictating the expected duration of safety and efficacy data requirements are discussed including the existing knowledge and safety database with a product, the intended duration of treatment, unmet medical needs, the natural history of the disease, and formulation/implant release factors. If studies enrol both BRVO & CRVO patients, results for each condition need to be considered separately. The chosen primary endpoint needs to reflect clinically relevant effects of treatment; situations where mean BCVA at a single time-point, mean average and responder are useful are discussed. The choice of comparator varies with existence of licensed alternatives and disease related factors. Non-inferiority studies against a licensed alternative must demonstrate assay sensitivity, with the choice of the non-inferiority margin also considering the maximum difference between treatments that can be considered clinically irrelevant. Companies should consider how they will advise clinicians on concomitant use of their product with laser and how these data will be generated given the timing of combination and delayed effects on efficacy.

Dry Age-related Macular Degeneration

Clinical Academic View: Adnan Tufail
Moorfields Eye Hospital Honorary Senior Lecturer, Institute Of Ophthalmology, University College London, UK

Age-related maculopathy (AMD) is a progressive disorder of the macula. The macula is the central part of the retina and has the highest density of photoreceptors which permit high resolution central vision. Photoreceptors produce waste throughout life and, with aging, the ability of the underlying cells – the retinal pigment epithelium (RPE) – to digest these molecules decreases. Excessive accumulation of waste (drusen) results in inflammation, photoreceptor and RPE cells degeneration and severe chorioretinal changes leading to severe visual loss. Clinical features of early AMD are drusen deposits and pigmentary changes of the RPE. The disease may abruptly evolve with choroidal neovascularisation (the exudative or “wet” form of AMD) or – way more frequently - slowly progress to geographic atrophy (the atrophic or “dry” form). Severe macular atrophic changes represent the final stage of the disease for both variants.

Dry AMD is a major public health issue because is the most common cause of legal blindness in the developed world and will become more prevalent with the expected increase of population aged over 80 years of age. Moreover, no effective treatment is currently available for dry AMD. Systemic risk factors for AMD include smoking, high serum cholesterol and age. Ocular risk factors are size of retinal area covered by drusen and RPE depigmentation/hyperpigmentation.

A very important issue is how to measure disease progression in clinical studies: there are structural and functional markers. With the Colour Fundus Photos (CFP) geographic atrophy was classically defined as all the sharply delineated lesion larger than 175 microns in diameter with apparent absence of RPE and visible choroidal vessels. With CFP, the natural history of dry AMD shows that geographic atrophy (GA) has an extension rate of 1-2 mm sq/year, with a median time to develop central GA of 2.5 years after diagnosis, when there is a visual loss of 3.7 letters initially and then 22 letters at 5 years. Fundus autofluorescence (FAF) photos showing RPE lipofuscin might be superior than CFP in detecting GA. Some autofluoresence patterns (the banded and the diffuse) demonstrated a higher rate of GA extension when compared to eyes without FAF abnormalities or focal FAF patterns. However, cataract might influence these patterns and a clinical trial would be of benefit in standardising this methodology. Optical coherence tomography (OCT) is a very promising tool to measure GA progression and show very early structural changes.

In clinical trials; the standard endpoint of high contrast visual acuity might be problematic because sometimes the GA extends sparing the fovea (non-central GA) and only lately will affect the fovea with evident central visual loss. Low luminance visual acuity and reading speed might be good alternatives, but the last one might be influenced by lesion size and position. Microperimetry is another way to assess outcomes in AMD: although is good in terms of global reduction of measurements and can predict progression of atrophy in presence of stable visual acuity (VA), it is not perfect yet in detecting local changes. Other functional outcomes include dark adaptation, contrast sensitivity and quality of life questionnaires but have some limits (i.e., relatively time consuming, not fully standardised, repeatability not well known in dry AMD).

Dry AMD is a major public health issue because is the most common cause of legal blindness in the developed world and will become more prevalent with the expected increase of population aged over 80 years of age. Moreover, no effective treatment is currently available for dry AMD. A very important issue is how to measure disease progression in clinical studies. The standard endpoint of high contrast visual acuity might be problematic: there are structural and functional markers. Colour Fundus Photos (CFP), OCT, low luminance visual acuity, reading speed, microperimetry, dark adaptation, contrast sensitivity and quality of life questionnaires, and their limitations are discussed.

Industry View: Oliver Zeitz
Ophthalmologist - Global Clinical Development, Bayer HealthCare Pharmaceuticals
Endpoints in dry AMD constitute a serious difficulty in clinical trials. In fact, visual acuity deteriorates very slowly in dry AMD and this timeframe exceeds the duration of development programs. Visual acuity reflects only a subset of vision changes in Dry AMD. More sophisticated changes are difficult to capture.

Drusen area and volume changes measured with OCT could be an interesting endpoint: over time, the number and size of drusen increases in patients with dry AMD and this could be useful in monitoring the disease before GA develops, although regression also occurs. Percentage of patients with decreased, stable and increased area or volume might be considered as an indicator of efficacy. Focus on subpopulation with particularly high risk of increase in drusen volume or area might reduce sample size in randomized clinical trials. The morphology of the drusen could also give some indication, since with spectral domain high-resolution OCT is possible to describe shape (convex/concave), internal reflectivity, homogeneity, presence of central core and overlying foci of hyper-reflectivity. A pilot study demonstrated with OCT that a commercially available drug might partially reduce the number of drusen.

Autofluorescence patterns might also be of interest because they might predict the progression rate (diffuse and banded patterns grow about 3 time faster). If the FAF signal at the junctional zone has prognostic character, changes of this pattern could be considered as a short-term indicator of efficacy.

GA area increases over time and can be assessed semiquantitatively and longitudinally and this is highly reproducible. This makes GA area extension suitable as an endpoint, in particular comparing two different timepoints. Changes in junction zone as an indicator of efficacy is also raised.

In searching for a valid comparator, we should consider that no treatment for Dry AMD is currently available and that the AREDS vitamin supplementation has slight effects on AMD progression. For oral and topical drugs, but also for injectables, a scheme with placebo with or without the AREDS formulation could be proposed.

The duration of the clinical trials needs to be adapted to the different structural endpoints. For instance, drusen morphology could be evaluated at 3-6 months for proof of concept and dose-finding studies and at 12 months for registration trials. The GA lesion growth could be measured at 18-24 months for registration purposes. Autofluorescence patterns could be used for proof of concept and dose-finding and potentially for registration; their baseline characteristics could be compared to the ones at 3-6 months.

It could be argued that visual acuity is not the preferred outcome measure for clinical development in dry AMD. Morphological parameters have been developed recently and are under evaluation and could be utilised as outcome variables soon.

Regulatory View: Marco Coassin
Retina Service, Department of Ophthalmology, University of Rome, Italy
The speaker particularly underlined that there are no validated surrogate endpoints. Further discussion with regulators at the development stage is recommended. All the future applications will undergo a

case by case evaluation at the light of the usual risk-to-benefit ratio considerations. In evaluating GA progression, no primary outcome for efficacy has yet been validated for dry AMD in an EU licensing procedure.

Primary endpoints should have clinical relevance for the patient and are usually "functional" (i.e., preservation of vision). Surrogate endpoints (anatomic and biomarkers) are the tests "reasonably likely to predict clinical benefit". It should be emphasised that an anatomical feature detected by imaging technology needs to be validated in order to be used in the clinical trials, requiring a very high correlation between the imaging endpoint and visual function. This was the case, for instance, when in patients with diabetic retinopathy a three-step change on the EDTRS scale correlated with a three-line vision loss. Dry AMD has some particular characteristics that make the central visual acuity an unfavourable primary outcome. In fact, GA lesions may have a relatively late effect on distance acuity (delayed till the foveolar involvement by GA); VA might not be sensitive enough to assess GA progression within a reasonable time frame in clinical trials; nevertheless, the speaker pointed out that that GA may also affect foveal vision early. In this latter case, a very small lesion might reduce the VA more than a large extrafoveal lesion.

The traditional method to evaluate GA, the Colour Fundus Photographs (CFP) has been shown to be reproducible in several clinical trials, including AREDS. It is not very good in discriminating between dead RPE and living but depigmented RPE. It also has a poor predictive sensitivity. It is objectively difficult to measure all the areas of atrophy and to include the most peripheral lesions. Moreover, it seems there may be different patterns of GA with different, unclear likelihood of progression.

Fundus Auto-Fluorescence (FAF) imaging seem to provide more information on GA than CFP. Several ongoing trials on GA have FAF as clinical endpoint and hyperfluorescent regions in peri-lesional areas at FAF were linked to increased rates of lesion growth. Several studies indicate that the lesion areas quantified with CFP and FAF are significantly correlated, but not equivalent. Although potentially useful, there are some unclear characteristics of FAF. Standard FAF seems overestimate foveal GA and underestimate extrafoveal GA when compared to Near InfraRed FAF (Pilotto et al. 2011). The fact that the loss of Near InfraRed FAF precedes the loss of FAF (Kellner et al. 2010) raises doubts. It is possible that irreversible degeneration of photoreceptor cells precedes changes shown by FAF and CFP. On this regard, SD-OCT showed early photoreceptor loss, while FAF corresponded to the linear disruption of choroidal hyper-reflectivity (Schmitz-Vandenberg et al. – only 21 eyes, no data on progression).

Besides progression of geographic atrophy, a number of other endpoints might be considered in dry AMD trials: progression to severe visual loss, progression to wet AMD, contrast sensitivity, low luminance VA, microperimetry, multifocal ERG, reading acuity and speed and quality of life questionnaires. Of note, there is no evidence that drusen regression subsequently results in a reduction in the risk of developing CNV, geographic atrophy or visual acuity loss.

On the regards of the appropriate length of follow-up in dry AMD trials, Sunness et al. (1997) suggested that to detect a 25% reduction in GA rate (α=0.05; power=0.80; losses to follow-up 15%), 153 patients per arm should be followed for 2 years in a placebo controlled trial. It is therefore advisable to have all patients continued until the last patient has the final visit at month 24.

Assessment of visual function is essential in describing outcomes from trials: GA area represents a morphological endpoint. Functional outcomes should be correlated with parallel imaging outcomes to support evidence of efficacy (sensitivity of the respective endpoints, correlation to functional loss, effective dosage). It would also be of interest to select a specified, particular GA population at high risk of progression in order to use visual loss as primary outcome (it is known that vision falls most rapidly in eyes with better baseline VA – i.e., VA>=20/50 had a 40% two-year rate of >=3 line VA loss [Sunness et al. 2008]). A subgroup analysis of different phenotypes of GA might demonstrate different progression rate for some subtypes. Enrichment of trials by patients at greatest risk of progression of GA into a separate trial would allow planning a shorter study. Ideally a spectrum of patients with different lesion sizes would be included to properly cover the later label. Because the mean change of growth is area size dependent, stratification methods or percentage of GA area change should be used. It is advisable to perform a responder analysis as well as to consider the parametric changes.

On the question of comparators for advanced therapies in GA, ideally could discriminate treatment effects with pharmacological interventions from release of growth factors deriving from the surgical intervention. However, the potential ethical difficulties deriving from risk to vision with sham surgery are highlighted as potential constraints on trial design.

No surrogate primary outcome for efficacy has yet been validated for this condition in a licensing procedure. Best corrected distance visual acuity may not be sensitive enough to assess disease progression within a reasonable time frame. Relevant secondary clinical/functional outcomes should be looked at closely in order to generate supportive evidence complementing the chosen primary endpoint. The clinical meaningfulness of the chosen endpoint should be justified. It might be possible to plan a trial with a suitable functional visual loss parameter as a primary outcome in an enriched population with greater risk of GA progression; implications for generalisabilty should be considered.

Report Day 2 Clinical Development, Scientific Advice

Uveitis

Clinical Academic View: Manfred Zierhut
Professor of Ophthalmology at the University Eye Hospital in Tübingen

Uveitis or intraocular inflammation can be classified according to localisation, (Anterior Uveitis, Intermediate Uveitis, Posterior Uveitis, or Panuveitis), morphology (granulomatous vs. non-granulomatous), aetiology and laterality (unilateral, bilateral). The goal is to classify according to aetiology although this is not always identified at an early stage, in order to discriminate infectious vs. non-infectious entities, those with or without associated diseases, traumatic and masquerade syndromes, and to better identify appropriate treatments. The Standardisation of Uveitis Nomenclature (SUN) working group defines criteria for Onset (sudden/insidious) Duration (limited: up to 3 months vs. persistent: longer than 3 months), and different courses of disease (acute: sudden onset with limited duration, recurrent: multiple episodes, separated by intervals without inflammation and without therapy of at least 3 months, and chronic: persistent uveitis with recurrences with less than 3 months free of recurrences after stop of therapy). Uveitis is a rare disease, with a uveitis total incidence of 35-50/100,000 inhabitants. This breaks down approximately as Anterior Uveitis: 50%, Intermediate Uveitis: 30% and Posterior Uveitis as 20%. Uveitis in Childhood is consistently at 5-10 % of all uveitis patients.

Evaluating signs and symptoms is important to help identify underlying aetiology and importantly any associated disorders. Symptoms are evaluated usually through history taking, questionnaires (symptoms) and Quality of Life (NEI VFQ-25), but there is no optimal uveitis “Evaluation of Symptoms” questionnaire. Evaluation of signs involves clinical investigations, and further targeted history taking, and targeted additional investigations such as FLA, ICG, OCT, Visual fields, ERG, CT, MRI, and laboratory diagnostics. Clinical investigations include visual acuity, slip lamp examination, intraocular pressure and funduscopy. Slit lamp examination is important for identifying aetiology, and complications such as cataract, secondary glaucoma, macula oedema, gliosis, traction, and neovascularisation- complications which make uveitis such as difficult and devastating disease. Additional investigations, depending on clinical findings include Laser Flare Photometry (LFP) which should play major role in future uveitis trials with validation data. Optical Coherence tomography (OCT) is useful for evaluating macular oedema. Fluorescein Angiography is used for assessment of issues such as neovascularisation and assessment of non perfusion. Perimetry is indicated where there is an unexplained reduction in visual acuity, or secondary glaucoma. Ultrasound is useful where there is possible posterior scleritis, vitreous bleeding, infiltrations, adhesions, retinal detachment, choroidal tumours or granuloma. Electrophysiology for the assessment of retinal function, is rarely indicated in uvetis, notable exceptions include birdshot retinopathy.

Diagnostic criteria have been published for the following entities: Behcet´s Disease (Int. Study Group for BD 1990), Acute retinal necrosis (Holland et al. 1994), Vogt-Koyanagi-Harada Syndrome (Read et al. 2001), Birdshot chorioretinopathy (Levinson et al. 2006). Further development is ongoing for Sarcoidosis (Herbort et. al 2009)(validation ongoing), Vasculitis (International Uveitis Study Group, ongoing) and Tuberculosis (Indian Uveitis Society, ongoing). In addition, the SUN-Project is developing a structured terminology for classification, to standardise terms and criteria for 28 entities. The grading systems available are the following: for AC cells these are– IUSG, SUN. For AC flare, there is Laser-flare-photometry but this is not validated. For vitreous haze, the NIH grading scale is still used - another new scale is being developed (Janet Davis). For macular oedema, OCT is available (but not evaluated). There is only one disease activity score available, Behcet´s Disease (Ben Ezra et al).

Treatment options include corticosteroids by various routes; topical, subconjunctival, parabulbar, intravitreal, and systemic. Immunosuppressives (systemic) are used mostly off label including Ciclosporine A, Methotrexate, Azathioprine, Mycophenolate mofetil, and Mycophenolic acid and others (Tacrolimus, Cyclophosphamide). Biologicals also are used for treating uveitis, off label, including anti-

TNF-alpha (Etanercept , Infliximab, Adalimumab), Rituximab (anti-CD 20), Daclizumab (anti-IL2-receptor, anti-CD25), Canakinumab and Anakinra (anti-IL-1), alpha-interferon 2a and beta-interferon. Problems of current medications for uveitis are that very few are on label (steroids, CsA, Osurdex) and side effects are notable. Therapies are particularly not well established for children. Unmet medical needs also are notable: absence of an optimal treatment against macular oedema, better outcome measures, more specific treatments for uveitis entities, laboratory parameters (regulatory T-cells, interleukin levels?) and biomarkers for disease control, more immunosuppressives on label, and steroid alternatives for anterior uveitis.

Regarding endpoints (EP) for uveitis studies suppression of inflammation is judged clinically meaningful in the following circumstances:

- anterior uveitis - reduction of 2 steps (e.g. 3+ to 1, 2+ to 0.5),
- intermediate and posterior uveitis - vitreous haze: 2 steps reduction.
- macular oedema - reduction (amount not defined, complete resolution is optimal),
- all types of uveitis: visual acuity: improvement of 2-3 lines (15 letters) and / or sparing of steroids (10 mg of prednisolone or less).

Primary Endpoints for anterior uveitis for active disease are: AC-cells (measured at 3 months) and for inactive disease recurrence rates optimally over 1 year. Endpoints for intermediate/posterior uveitis active disease are vitreous haze (3 months), and for inactive disease: recurrence rates over 6 months, optimally 1 year). Secondary endpoints include visual acuity, sparing of steroids, macular oedema (OCT, FLA), AC-cells (3, 6 months), and Quality of Life (NEI VFQ-25).

Uveitis is a heterogeneous group of diseases making trials difficult. There is a need for better definition of entities and further validation of endpoints, and more randomised controlled trials with well-defined uveitis entities and specific endpoints dependent on aetiology. Longer follow up in studies is needed (recurrences: 1 year). Children with uveitis should also be involved in studies. Damage tends to develop with inflammatory activity; control of this inflammatory activity is the most important goal of treatment. Endpoints should reflect activity of inflammation as visual acuity is not always a good primary endpoint.

Industry View: Robert Kim
Clinical VP, GSK

The target population is mainly chronic non-infectious uveitis- an orphan indication affecting < 4.8 in 10,000 persons in the EU. Intra-ocular inflammation is heterogeneous, with between 30 and 70 different entities. Treatment (EU) comprise steroids as the mainstay, Ciclosporin, and off-label use of immunosuppressives. Heterogeneity in the target population of 30- 70 syndromes, can be managed by "Lumping" these into manageable categories with an emphasis on location and tempo of inflammation. The target population can also be managed by "Splitting" where there are specific uveitis entities with defining characteristics; for example Behcet's disease characterised by explosive recurrent attacks of occlusive vasculitis, Vogt-Koyanagi-Harada syndrome by serous retinal detachments, Birdshot retinochoroidopathy by typical electroretinographic abnormalities, and scleritis where intra-ocular inflammation may be secondary.

An understanding of the biology of disease and pharmacology of the agent can suggest which approach to take; however, with initially a wide net in phase 2, and then it can be appropriate to split in later development. A key clinical issue is steroid side effects. Steroids are effective treatments for uveitis locally and systemically. A challenge is managing steroid side effects with prolonged or recurrent treatment. Such patients constitute an unmet need.

For endpoints in uveitis, visual acuity remains an unambiguous indicator of clinical benefit, however VA not the most sensitive indicator of effect as improvements in VA can lag behind improvements in inflammation control and be confounded by other factors. More responsive endpoints are measures of inflammation. 5 step scales for anterior chamber cells and vitreous haze are available. Both Clearing (0) and Improvement (2-step) are relevant. For steroid sparing, a desired endpoint would be complete elimination of topical or ocular injection therapy. However, it is often difficult to eliminate steroids completely but a decrease to ≤10 mg prednisone equivalent/day or less is recognised as beneficial.

Reduction of recurrence rates and remission may be appropriate endpoints depending on the indication but require longer studies. Regarding macular oedema, correlations with visual acuity are weak, however recent preliminary work suggests that a clinically meaningful threshold for change in uveitic macular oedema evaluated by OCT appears to be 20%. This is based on a study examining sensitivity and specificity associated with a 10 letter threshold gain or more and changes in macular thickness

based on OCT responses. Other potential novel endpoints are being developed. Many patients are managed with combination therapy. For these patients, a score value can be applied to reflect the total immunosuppressive load. In scleritis, a problem has been a lack of a consistent grading system. A grading system has been developed has been developed as a disease activity score rather than a measure of a therapeutic intervention, but this is a logical next step.

Regarding comparators, in uveitis trial, placebo is usually not possible, particularly with new active disease. A particular challenge is that standard of care includes off label use of many medicines, and that there is no uniformly accepted standard of care. There are two basic paradigms; to control active disease, either as new or recurrent, and to reduce steroid/immunosuppressive dose(s) required to control disease. Clinical trial design for active disease necessitates head to head (vs standard of care, usually steroids). In the setting of steroid (or immunosuppressive)-sparing, with controlled disease, an add-on study [Drug + Steroid] vs [Placebo + Steroid] with steroid tapering would be foreseen.

For duration of studies, it is suggested that in a new indication for a previously approved drug: ≤ 1 year safety data would be sufficient. For a new molecular entity: at least 1 year of safety would be needed. Recommendations for sustained-release formulations will vary depending on duration of release. For efficacy data, study duration would depends on type of uveitis. For anterior uveitis, 3 months efficacy data would be needed. For posterior uveitis, a duration of 6 months would be the minimum foreseen. For alterative Special cases, e.g. Behcet's, Vogt-Koyanagi-Harada: 1 year efficacy data may be needed.

Managing heterogeneity is difficult and needs an understanding of: disease pathogenesis, mechanism of action of drug, and possible responsive subpopulations. Various endpoints are available when planning how to handle rescued patients, this can be an endpoint in itself where endpoints of recurrence or remission is being evaluated.

Where a dichotomous endpoint, e.g. responder analysis is being used, rescues can be scored as failures. With a continuous endpoint, e.g. VA score, it may be possible to use intent to treat with last observation carried forward although this may be problematic with progressive disease. Sensitivity analyses using per protocol population should be carried out.

In developing trial designs for uveitis, heterogeneity in uveitis syndromes, the lack of accepted standard of care, and knowledge gaps in understanding the biology represent significant challenges.

Regulatory View: Karl-Heinz Huemer
Assessor, AGES AT, Alt member of PDCO and SAWP

The aim of this talk is to trigger discussion of more contentious issues, rather than give definitive regulatory positions. Regarding which endpoint for uveitis can be acceptable, primary endpoints should be clinically relevant showing direct patient benefit with a preference of visual function outcomes.

In CHMP Scientific Advice for uveitis, best correct distance visual acuity (VA) has been repeatedly proposed/accepted as primary, co-primary or key secondary endpoints. However: this will depend on feasibility and treatment duration. Examples, in disease stages with irreversible (chronic) visual damage improvement often cannot be expected, but VA is still relevant to examine possible further deterioration. In short trials (acute disease) VA change might be less suitable as primary outcome, but is still a relevant secondary outcome. It is expected that change amplitude will have to be estimated for power calculations. As composite measure, VA is also often included in recurrences definitions.

SUN criteria have also been accepted as surrogate endpoints. Endpoints could include the full parameter list, or selected only elements. Examples are provided below.

- Vitreous haze (standard 5 unit scale (0-4+) has been accepted in a particular acute setting by the scientific advice working party in the context of support with other secondary endpoints including visual acuity with a preference for a primary endpoint at 4 weeks.
- Anterior chamber (AC) cells (5 unit scale) after 4 weeks was not supported for moderate disease stages in a chronic setting.

These criteria are possible as continuous measures or as a threshold for recurrence definition; e.g. vitreous haze and AC cells ≤0.5 after 24 weeks, with no increase ≥2 AC cells, ≥2 VH, no decrease ≥10 ETDRS within this period. There is a need to exactly specify the criteria to match the included patient population (e.g. with regard to population homogeneity, disease severity and course of the disease).

Corticoid-sparing outcomes are also welcome in patients with a need for continued steroid treatment but it is necessary to specify the standard of care (SOC), dosage range, and steroid tapering schedule. Endpoints like the proportion of patients receiving >10 mg corticosteroids has been agreed. Recurrence rates as an endpoint are considered highly relevant, but need to exactly defined (e.g. > 0.3logMAR change in VA, a specified change in vitreous haze and/or AC cell numbers, macular oedema). Recurrence rates alone might not cover more harmful or prolonged progression and deterioration. The frequency of recurrences is preferred to time to first 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), or other clinical parameters such as intra-ocular pressure, macular oedema, cataract or other uveitis complications.

An appropriate trial duration will depend on chosen endpoints and proposed indication. Examples are provided below. For chronic uveitis, trial durations of 24 weeks treatment plus 12 weeks safety follow up have been accepted (16 weeks treatment was considered too short). 24 weeks including safety follow up has been accepted for a line extension where other indications have already been 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 weeks rather than the proposed 6 wks. Anterior chamber cells (5 unit scale) after 4 weeks was not supported for moderate disease stages in a chronic setting.

For an induction label, (treatment of acute disease), a feasible short time efficacy outcome should be planned. Maintenance labels will require long term efficacy data. For a planned indication of both induction and maintenance, the proposed efficacy endpoint at 24 weeks was considered much too long for induction, and too short for maintenance. Additionally different inclusion criteria may be necessary. 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 (more homogeneous population). Broad label claims can be supported, but might be methodologically more challenging, e.g. consider anterior uveitis in a separate trial (for methodological reasons). There is a need for clear definitions of disease criteria, aetiology, prior and concurrent treatments and resistance to steroids. The population should reflect proposed claim, and should be sensitive, and feasible.

Comparators: To position a drug on the market, an active comparator is preferred. This is challenging when comparators are off label, but aiming for superiority can be considered. Placebo might be acceptable for chronic quiescent disease e.g. a placebo comparator (sham injection) has been accepted for intermediate uveitis (slower disease progression). Placebo-add on to corticosteroid will raise less concerns, but would be reflected in the later label claim. Allowable concomitant therapies, specific application systems and specific dosage regimens, should be defined. The criteria and nature of rescue medication should be specified in addition to plans for handling these patients in the analyses.

Different trial design proposals might be considered as valid, depending on the exact disease definition and the claim targeted. This has consequences with regard to endpoints, treatment duration, acceptable controls, and inclusion/exclusion criteria. Many parameters could be justified case by case. Biomarker qualifications procedures are recommended for novel methodologies. Open questions for guidance include: managing standard of care including off label use, and absence of a uniformly accepted SoC, population definitions, appropriate steroid sparing endpoints, the choice of comparator, the most clinically relevant endpoints, the role of macular oedema as an endpoint, continuous or dichotomous data for the primary analysis, handling of combination treatments and rescued patients.

Ocular Surface Restoration

Clinical Academic View: Per Montan
Associate Professor, Department of Ophthalmology, St Eriks Hospital, Stockholm

Dr Montan highlighted the underlying indications, and frequencies of corneal grafting. Graft success aims for a clear visual axis in the corneal graft with vision of 20/40 or better; rates of success at 10 years are expected to be around 70%. The risk of corneal graft rejection is lifelong. Topical steroids have long been the backbone of prophylaxis and treatment of corneal graft rejection, although the best regime has not been defined and few RCTs exist. Adverse reactions such as increased intraocular pressure are well recognised. Risk factors for rejection have been identified but can have different impacts; such as indication for graft, co-morbidity, a vascularised recipient bed, young age of recipient, and previous rejections. In managing high-risk grafting, tissue matching has had contradictory results- HLA Class I matching may be beneficial while HLA Class II matching may be

detrimental. Add-on oral immunosuppression has often been used in uncontrolled studies; no solid conclusions can be reached, with furthermore a lack of protocols combining 2 immunosuppressants. Regarding adjunctive topical immunosuppression, topical ciclosporin or topical tacrolimus, both may replace steroids in IOP-responders, but any add-on benefit is unknown, and there are no licensed products for such ocular use. A new therapeutic approach is to target new vessels, as preconditioning.

Potential clinical trial design parameters for high-risk corneal grafting could include; observer masking, treatment with standard of care with topical steroids, aim to assess an add-on regimen and avoidance of heterogeneous populations. Potential efficacy endpoints could include frequency of rejection episodes within 2 - 3 yrs, graft transparency, vascular activity, visual acuity. Pachymetry and endothelial cell density may also be of value together with a visual function questionnaire. Safety variables include ocular (surface, IOP) and systemic (haematology, liver, kidney) effects. Techniques using Scheimpflug imagery to provide objective measures are possible. Other ways to avoid rejections include lamellar grafting; thus avoiding full thickness penetrating keratoplasty if possible.

Limbal stem cell (LSC) deficiency are found in rare conditions such as Stevens-Johnsons syndrome, ocular cictricial pemphigoid and aniridia, and also followings severe ocular chemical burns. Dry eye is a contraindication to any surface restoration project. Restoration possibilities include autologous stem cell transplantation for patients with unilateral disease, or allogeneic limbal stem cell transplantation. Ex vivo expansion of limbal stem cells (LSC) involves the migration or separation of LSCs from a small limbal biopsy on a carrier. Animal products are usually involved however transfer to the recipient eye is easier and there is limited use of autologous eye tissue. Cultivation takes place in licensed cell laboratories.

Success of LCS grafting s thought to be a stable and avascular surface with published results indicating success rates for autologous grafts of 75 – 100%, with explants similar to cultivated cells, and for allogeneic grafts of 30 – 75%. Remaining poor vision may be restored with keratoplasty. Potential trial design parameters include observer masking, possibly comparing explant vs. culture, or culture vs. culture? Different immunosuppressive protocols for allogeneic transplants would probably be needed. Efficacy endpoints at 1 - 2 years would include corneal epithelial parameters (vital staining, superficial transparency, regression of vessels, possibly impression cytology), VA, pain, photophobia, VF questionnaire. Data on safety parameters would also be essential.

Unmet needs in restoration of the ocular surface include the best topical steroid regime for low-risk grafts, the add-on value of topical immuno-suppressants and/or anti-angiogenic treatments, the value of systemic immunosuppression and HLA-matching in high-risk grafting and allogeneic stem cell transplants, and the development of gold standard cultivation of (limbal stem cells) LSCs. Potential clinical trial design parameters, including endpoints for high-risk corneal grafting and LSCs are proposed.

Industry View: Giovanni Milazzo
Clinical Regulatory Manager Chiesi Farmaceutici

Dr Milazzo was asked to address the challenges and approaches in clinical development of limbal stem cells from the industry perspective. The first challenge is that limbal stem cells deficiency is a rare condition (Orphan condition at less than 0.5 /10.000) and most common in the adult population. An open question is whether the paediatric population should be excluded from the efficacy and full safety analysis with the advantage being that this would allow completion of the clinical development without delaying the possibility to treat the adult population. The disadvantage would be that this would lead to the exclusion of the paediatric population from the therapeutic indication.

How should the severity of LSC deficiency be graded?. It is suggested that vessel penetration of 2-3 corneal quadrants or more with involvement of the central cornea equates to 'Total' LSC deficiency with 2 clock hours or less of surviving limbus; should other criteria be considered such as a minimum accepted duration of the disease, full conjunctivalisation or a negative outcome of repeated full corneal transplantation?

The trial design is a challenge as there is no suitable reference treatment: neither placebo nor full corneal transplantation are suitable. It is considered that randomisation is not possible. However the potential for bias needs to be minimised. Where the trial design is open-label, objective end-points, with independent efficacy evaluation using two assessors, and masked evaluation of efficacy based on photographs should be considered. There is a risk of discrepancies in the judgment between the investigator and the external assessor, and masked evaluation is possible only for efficacy parameters evaluable on photographs.

The most appropriate endpoint of efficacy is restoration of the corneal epithelial integrity. The restoration of a stable and intact corneal epithelium means a resolution of symptoms (pain, photophobia), inflammation and the improvement of visual acuity in patients without scars of the corneal stroma. It is questioned whether an intact corneal surface (by fluorescein stain) with absence of corneal superficial neo-vascularisation can mean restoration of the corneal epithelium. Both parameters are indirect expression of the restoration of limbal stem cells. Both parameters can be evaluated on photos by independent assessors and both parameters are easy to evaluate in the routine activity of the clinical centres. However both parameters can give false positives (i.e. concomitant herpes infection), do not directly indicate a corneal phenotype which is the proof that the limbal stem cell transplantation has restored a self-generating corneal epithelium and some patients might not derive a tangible clinical benefit from having a stable corneal epithelium. Therefore, which other parameters can be used to evaluate the restoration of the corneal epithelium? Should corneal phenotype be assessed in addition by corneal impression cytology, or by in vivo confocal microscopy. Impression cytology directly identifies corneal and conjunctival cells but it does not provide information on the overall corneal surface. It also requires multiple sampling for complete mapping, is a complex and delicate technique, often producing unreliable results with a risk of inadequate sampling. It causes significant discomfort with risk of refusal by the patient and carries a risk of ocular surface damage in patients with partial restoration of epithelium. In-vivo confocal microscopy results correlate well with impression cytology findings but there are disadvantages such as difficulties when there is a narrow interpalpebral aperture, poor tolerance with severe ocular surface disease, that this is a complex, non-standardised technique which is not widely available in surgical centres and requires expert, dedicated personnel to provide reliable findings from a complete mapping. It provides information on cell morphology and density, but not on epithelial cell type (corneal vs conjunctival) and the approach is more time-consuming than impression cytology.

When should the restoration of a stable and intact corneal epithelium integrity be evaluated? The half-time of corneal epithelial replacement is 9 weeks (Sharma A, 1989). Theoretically, the restoration of a stable and intact corneal epithelium might be established 6 months after the LSC transplantation, however, failure of LSC transplantation has been reported also between 6 and 9 months from transplantation (Rama P, 2010). Other important variables include symptoms, quality of life, corneal epithelium transparency, visual acuity, and outcome of the full corneal graft. Duration of follow up for safety requires data on short term (surgery, inflammation, immunoreactions) and long term aspects (tumour formation, infections), and should be at least 6 months for chronic treatments (CPMP/ICH/375/95). Also, it should be considered if true cumulative incidence is <3% if no SAE reported during 12 months exposure in 100 patients (CPMP/ICH/375/95) and possibly longer. In conclusion, patient's unmet medical need, and the need for evidence should be balanced such that hurdle for licensing should neither be too high nor too low.

Challenges for industry in the development of limbal stem cells are that the target disease is a rare condition, the severity grading of which is not established, that there is no suitable reference treatments, that the optimum approach to minimise the potential for bias remains to be established in addition to the most appropriate endpoint of efficacy.

Industry View: Claus Cursiefen
Chairman and Professor, Department of Ophthalmology, University of Cologne

Professor Cursiefen discussed surrogate endpoints in the prevention of graft rejection, and potential methods to grade and quantify corneal neovascularisation. The cornea is normally avascular. There are common core molecular pathways of pathological corneal neovascularisation despite different causes such as inflammation, hypoxia, surgery/suture material and limbal stem cell deficiency. These common mechanisms are: upregulation of VEGF (via inflammation and hypoxia): central step independently of underlying cause. IRS-1 is the up-regulatory switch necessary for pathological over-expression of VEGF and neovascular proliferation. The consequences of neovascularisation for the patient are: blindness/ decreased visual acuity and a high risk of corneal graft rejection. With neovascularisation, the immune privilege of the cornea is lost, leading to 0-50% rate of 10 year graft survival in contrast to >90% with a low risk corneal graft without neovascularisation. Graft failure and graft rejection risk increases with the number of corneal quadrants affected by neovascularisation before keratoplasty (Bachmann, et al Ophthalmology 2010). Social and economic consequences are that regrafting, if undertaken, is expensive. There is the individual health burden of patient with possible unemployment and absence from work. There are costs for surgery and transplants, waiting lists and side-effects of systemic immunosuppressants.

Cursiefen et al., Br J Ophthalmol 2011 published a consensus statement on the indications for anti-angiogenic therapy in the management of corneal diseases associated with neovascularisation; which was an outcome of an expert round table. This identified unmet medical needs in corneal

neovascularisation management pre- and post-keratoplasty. 10% of corneal transplants /year in the EU are high-risk with 50-100% rejection rate despite local and systemic immunosuppressants. There is no effective therapy so that often surgery is not performed. Current management options are insufficient being steroids (which are only partly effective, and have major side-effects) and Anti VEGF strategies (which are off-label, have stability issues and side-effects). New treatment approaches are needed for example Anti IRS-1/VEGF strategies - currently in clinical trials.

Strong preclinical evidence suggests that anti-angiogenic therapy promotes graft survival. There are different possible timings and aims of anti-angiogenic interventions. Anti-angiogenic therapy is proposed prior to keratoplasty as PRECONDITIONING for primary prevention such that there is inhibition of angiogenesis for example during keratitis. Secondly, anti-angiogenic therapy is targeted prior to keratoplasty as PRECONDITIONING for secondary prevention such that there is angioregression prior to grafting. Furthermore, data are presented to show that anti-angiogenic therapy after low-risk keratoplasty promotes graft survival.

Parameters of potential study designs; inclusion criteria require specification and these will depend on the setting of the study (i.e. pre-/post-keratoplasty). For the pre-keratoplasty setting: stromal corneal new vessels should be present and documented in intended graft area. For the post-keratoplasty setting: inclusion criteria depend on whether the intervention is intended to treat or to prevent corneal new vessels or corneal graft rejection (CGR). For treatment, post-keratoplasty patients who develop active stromal neovascularisation or with active CGR should be included. For prevention, recipients at high risk of corneal graft rejection should be included in initial studies. Subsequently, a broader population (mixed risk for CGR) may be chosen for inclusion in clinical studies. Inflammation should be controlled with steroids as appropriate.

Endpoints should also be specified. While Visual acuity (VA) is the standard endpoint in ophthalmology there is no correlation between anti-angiogenic therapy and visual acuity since a large variability of factors, including surgical technique, affecting visual acuity after transplantation. Visual acuity would appear not to be the most appropriate endpoint for products treating angiogenesis. Graft rejection would not appear to be appropriate for primary prevention because of the long duration of study time of initial therapy, delay until transplantation, and late occurrence of graft rejections. It is also difficult to assess in modern lamellar grafts.

Anti-angiogenesis is a mechanistic endpoint, a reliable measurement, and valid for both types of preventions, and the most relevant primary endpoint to demonstrate efficacy of anti-angiogenic agent in patients with proliferative CNV uncontrolled under the current best available therapy. This may be proposed as a “biomarker” for a conditional approval given the strong medical need, which is then confirmed by long-term graft survival data (thus validating CNV as surrogate endpoint). Standardised quantification of corneal neovascularisation is possible. Semiautomatic image analysis of standardised slit-lamp pictures is possible with image analysis software. This has high sensitivity and specificity due to low background noise and is a reliable technique developed for and already used in phase II and III trials of topical anti-angiogenesis at the cornea.

There is an unmet medical need with no specific licensed medical treatment for corneal neovascularisation (CNV), particularly in the context of corneal transplantation. It is proposed that inhibition of CNV is the most relevant primary endpoint to demonstrate efficacy of anti-angiogenic agents in patients with proliferative corneal new vessels uncontrolled under the current best available therapy and furthermore that this supports benefits for the patient in preventing the need for a corneal graft, as well as improving graft survival if transplantation becomes necessary.

Regulatory View: Gopalan Narayanan
SAWP/CAT member, Clinical Assessor, UK Medicines & Healthcare Products Regulatory Agency

The regulatory perspective of development of advanced therapies with limbal stem cell as a particular case study was discussed. This included surrogate endpoints as opposed to clinical outcome, duration of clinical trials, and comparators. From a clinical regulatory perspective, product features are important. The mode of action is important in predicting clinical behaviour. The definition and quality of biopsy material is essential. The process of manufacturing, starting materials e.g. foetal serum and risk of exposure to animal borne diseases, are reviewed critically. The nature of the product - autologous as opposed to allogeneic, release testing, (as standard release tests may not be possible), transport/storage (z effects on viability of cells) are taken into consideration and how these impact on efficacy/safety. For scaffolds/devices, whether these are integral or not, needs to be established. A classification procedure can be undertaken where doubt exists.

The regulator will consider the aim(s) of therapy. For example, with a symptomatic benefit; is a benefit of this nature sufficient to justify potential risks of treatment? Restoration of integrity may be accepted as a primary endpoint but requires individual justification in a given circumstance. In the case of LSCs, it is noted that improvement in visual acuity requires a possible secondary step, when stromal scarring is present.

Early phase studies need to be tailored to the process. Animal studies/ homologous models/translatability of models should be discussed. Biodistribution, migration, persistence are important issues. Tolerability, proof-of-concept, and dose-finding studies can be problematic but feasibility should be assessed, discussed and the approach justified.
For confirmatory studies, dose rationale and posology need to be discussed and justified considering factors such as number of cells, area of replacement, single and repeat treatment, immunosuppression protocol(allogeneic), surgical technique, training, or restrictions on prescribing.

For a comparator, regulators prefer concurrent controls be they placebo, active control or standard of care. Historical controls, or uncontrolled studies are subject to bias and require case be case justification.

Regarding end-points in confirmatory studies for limbal stem cell deficiency, corneal epithelial integrity has been accepted based on conjunctivalisation (evaluated through staining, impression cytology for goblet cells, or con-focal microscopy) and neovascularisation extent. Methodology should be discussed in relation to photographic compared to clinical evaluation of new vessels. Visual acuity is an important secondary endpoint although limitations are acknowledged given stromal scarring. However, the extent of improvement, durability and possible deterioration in visual function should be addressed. Evaluation should be as unbiased as possible though Investigator / Independent committee masking. Symptomatic improvement should be assessed although variability in symptomatology (irritation, discomfort, pain, watering.) is also recognised. Follow-up should be 12–24 months or until corneal graft is undertaken if shorter, and should consider safety issues such as tumours, and infections. Persistence of efficacy and success of future full-thickness graft should also be considered.

Open questions for guidance: the best methods to assess severity of limbal stem cell deficiency, and corneal surface restoration, and the duration of long term follow up needed. Also, the acceptability of corneal neovascularisation as an endpoint for primary or secondary prevention of rejection in corneal grafting or for angioregression is not yet established. Formal submission of biomarker qualification advice or opinion is recommended for novel methods such as corneal neovascularisation as an endpoint in confirmatory trials for corneal graft rejection, or methods to assess severity of limbal stem cell deficiency.

Dry eye disease

Clinical Academic View: David Sullivan
Associate Professor Harvard Medical School Schepens Eye Research Institute of Boston, Mass, US
The definition of dry eye disease is: “Dry eye is a multifactorial disease of the eyes and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.” (TFOS DEWS, 2007). Dry eye disease (DED) has no cure. DED is broken down into two major categories, aqueous deficient due to reduced lacrimal flow and evaporative due to meibomian gland dysfunction. In both cases, this leads to tear hyperosmolarity which further leads to tear film instability. With high hyperosmolarity, symptoms evolve and sheer stress leads to loss of goblet cells and epithelial damage with stimulation of proinflammatory factors.

The reported prevalence of DED ranges from approximately 5-15 % in the USA, Australia and Europe (Spain) to 30-50% in Asia, the highest prevalence observed in subjects of Asian and Hispanic origin. DED is more common in women and the prevalence increases with age. DED also affects the quality of life and the impact of fairly severe dry eye has been reported comparable to dialysis and severe angina (comparisons of time trade off models). DED leads to problems with reading, computer use and work performance. There are very few approved pharmacological treatments for dry eye in the world. The currently explored treatment targets are mucin deficiency, aqueous tear deficiency, lipid deficiency and ocular surface damage with several compounds in development.

The major challenge in the development of treatments for DED is that the common signs and symptoms do not correlate. While the most common endpoints to evaluate signs of DED in clinical

trials today are the Schirmer test and corneal staining, their diagnostic value is limited. Existing treatments fail to address causative mechanisms and evaluation of symptoms cannot be used alone to track severity. In recent studies, it has been shown that the Schirmer score and tear film break up time (TBUT) correlates well in severe eye disease, but not at all in moderate and mild disease. It has also been shown that 30-40% of mild to moderate dry eye patients have no corneal staining, while a number of healthy subjects have corneal staining. Also the Ocular Severity Disease Index (OSDI), validated for use in dry eye disease, shows a poor correlation with other ocular severity index. Consequently, with the exception of severe DED, it is very difficult to stage severity of patients with these tests which also translates into questions on reliability in terms of evaluating efficacy in clinical trials. Repeatability between clinical trials has also been poor. We need outcome measures reflective of the disease. Tear hyperosmolarity is common across all forms of DED and has been recognised as the central pathogenic mechanism of DED. Tear osmolarity has been demonstrated to correlate with symptoms (VAS), TBUT, corneal staining and Schirmer's test.

In order to develop new treatments for dry eye, we need new diagnostic approaches to help solve the puzzle. Potentially, tear osmolarity may be a marker that can be used to evaluate efficacy in clinical trials, but we definitely need others as well.

Clinical Academic View: Meibomian Gland Dysfunction, Kelly Nichols
Professor, University of Houston, College of Optometry, US

Meibomian Gland Dysfunction (MGD) has an impact on the core mechanisms of DED. This has been overlooked until recently and the impact of MGD in DED was first described in 2006, although the description of MGD was vague. Therefore, the International MGD Workshop, sponsored by TFOS, was conducted. Its outcome was published in March 2011 (IOVS) and summarised in this talk. The meibomian glands are large sebaceous glands with no direct contact to hair follicles and located in the tarsal plates of upper and lower eye lids. Its definition was established by the MGD Workshop: "Meibomian Gland Dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterised by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease." Not all cases of MGD have an associated lid inflammation or posterior blepharitis. MGD can be a low or a high delivery states, the most common being the obstructive form. The few studies on the prevalence of MGD indicate figures of 40 - 60% in Asia and 5 to 20% in Australia and USA. However, definitions of MGD have varied between studies and potentially also conditions for evaluation.

Factors related to MGD include contact lens wear, chronic blepharitis, Demodex folliculorum, aging, androgen deficiency, Rosacea, Sjögren's syndrome. Medications commonly associated with the condition include isotretinoin, antiandrogens and antidepressants. There is an overlap of general DED symptoms and clinical signs of MGD, but limited data is available. The MGD Workshop presented an algorithm for clinicians to diagnosis the disease with four severity stages based on evaluation of symptoms and clinical signs that include secretion and ocular surface staining. There have been no validated symptoms surveys and expression of the glands to evaluate the secretion has not been widely accepted. Evaluation of the lid has been done in clinical trials but without any standardised approach and there is no consistency in terms of grading scales. Better tests to evaluate and grade MGD are needed.

The current practice patterns to treat MGD include lid hygiene, warm compresses and lid massage, but there is no consistency how this should be done. Lubricants, including those containing lipids, are frequently recommended. Topical and systemic antibiotics are often recommended in moderate to severe cases with anti-inflammatory treatment and surgery in the most severe cases. The MGD Workshop recommended using the severity staging to guide treatment.

At the time of the MGD Workshop, there were few published reports of clinical trials in MGD. The majority were small and of short duration, only three were randomised and controlled. The criteria to include subjects were not uniform, but commonly included evaluation of lid changes and symptoms. Also outcome measures varied and besides evaluation secretion/expression, gland obstruction, eye lid appearance and lipid layer, most endpoints were similar to those used in clinical trials in general DED.

It was concluded that there is a high need for additional randomised, controlled, double-masked treatment trials with clearly defined objectives, relevant outcome measures based on pathophysiology, and refined inclusion & exclusion criteria. There is also a need to further characterise the natural history of MGD and to gain further understanding of the association with dry eye disease. A development and validation of a symptom questionnaire specific to MGD would be welcomed.

Clinical Academic View: Anthony Bron
Professor emeritus, Nuffield Laboratory of Ophthalmology, University of Oxford, UK
There is no role for biomarkers in screening for dry eye in the general population but biomarkers could be of value in predicting dry eye risk in defined subgroups such as contact lens wearers, post-LASIK surgery, after bone marrow transplantation and so on.

A number of symptom questionnaires have been validated and there have been attempts to combine measures of symptoms and of ocular surface pathology to generate severity scores (Sullivan 2010). There has been some promise in this area but overall there is a poor correlation between symptoms and signs. Currently, no questionnaire is available which will detect symptoms arising from Meibomian gland dysfunction (MGD) alone. This is a major omission, since MGD is the chief cause of evaporative dry eye and the sensitivity of the lid margin is of a similar to that of the central cornea.

One reason for the mismatch between symptoms and signs may be that there are multiple potential sources of symptoms, which may vary in importance according to the stage, duration and severity of DED. These include tear hyperosmolarity, increased surface shearing due to mucin deficiency and reduced lubrication, direct damage to nerve endings causing altered nerve excitability or neuropathic firing and the release of algaesic mediators. To be of value, a biomarker should reflect the mechanisms of ocular surface pathology and scale with disease severity.

The effect of sampling procedure on biomarker measurement
Dry eye biomarkers are measured in the tears and in epithelial cells from the ocular surface. Because tear sampling may induce reflex tearing, biological variability may be high and sampling methods require rigid standardisation. Also, the quality and quantity of tear biomarkers is affected by the method used. Some factors which influence measurements are given here:

Tear samples collected rapidly with glass capillaries contain less plasma protein and epithelial cell contaminants than tears collected with absorbent materials such as filter papers. However, where tear volumes are low, (as in aqueous-deficient dry eye-ADDE), high collection times increase the risk of contamination and claims that the capillary method is non- or minimally- invasive may be illusory. Available tear volume varies and in ADDE, volume will be progressively low while in evaporative dry eye (EDE), where lacrimal function is normal, it could be normal. The difficulty of collection in ADDE may influence tear biomarker concentration.

With filter papers and sponges, collection is less vulnerable to low volumes but exact volume, which is relevant to protein concentration, is difficult is to measure. Also, the degree of protein and cell contamination will vary.

Many analytical techniques in current use require several microliters of tears to perform analyses. Techniques are needed that use nanolitre samples to increase speed of collection and to reduce cell contamination and reflex dilution thereby improving precision of the method. For example, measurement of tear osmolarity can be performed on a 50 nL sample. The value of comparing biomarker ratios within single samples has not been fully exploited but has been used to track the ratio of Th1 and Th2 type cytokines in a study of dry eye (Lam 2008).

Conjunctival Epithelial Cell Samples are regularly used to quantify inflammatory events at the ocular surface and the approach has been refined by the employment of flow cytometry. Methods include conjunctival impression cytology (CIC) which provides an instantaneous regional sample including goblet cells, or brush cytology where the cell source is more diffuse. Analytical methods include histochemistry, immunocytochemistry, and measurement of mRNA transcripts.

Biomarker technologies
A wide range of technologies have been used to characterise tear proteins and other molecules in the tears, including: 1D and 2D electrophoresis, the ELISA sandwich technique, protein arrays, Western blot, LC-MS, SELDI/TOF, MALDI/TOF proteomics and nanoLC -nano ESI-MS/MS. Interest has been directed to cytokines, chemokines, adhesion molecules and other molecules.

In the search for biomarkers for dry eye, there is particular interest in those which relate to its clinical features. Measurements of tear and conjunctival epithelial mediators have shown that increased levels of IFNγ-inducible chemokines (eg CXCL 11) have been associated with low basal Schirmer values, low tear clearance, reduced goblet cell numbers and kerato-epitheliopathy, (Yoon 2010). Other studies have observed an increase in the ratio of markers for Th1 (IFNγ-) versus Th2 (IL-13) cell activity and an increase of tear MMP9 correlating with conjunctival epithelial mRNA transcripts for IL-1β, IL-6, TNFα

and TGFβ1. The latter cytokines are known to stimulate MMP9 production, and MMP9 in turn, cleaves and activates IL-1β precursor and latent TGFβ. MMP correlated with a measure of clinical severity (Chotikanovich) and may useful to track dry eye activity. However tear MMP9 or proMMP9 levels are increased in other ocular surface disorders.

Another study used protein chip array technology for biomarker detection in tear fluid collected on Schirmer strips. There was some promise of diagnostic value in dry eye. Multivariate discriminant analysis was used to identify about 50 peaks with a significant difference between DE and controls, and further discriminant analysis revealed a cluster of 7 polypeptides which, used in diagnosis, offered a sensitivity and specificity of around 90% at a false positive rate of 10%. (Grus 2005). In a promising study ITRAQ technology was combined with 2D-nanoLC-nanoESI-MS/MS quantitative proteomics to demonstrate 6 up-regulated proteins and 4 down-regulated proteins in dry eye patients. Using a 4-protein biomarker panel, the diagnostic accuracy for dry eye was 96% (sensitivity, 91.0%; specificity, 90.0%). Three proteins correlated with disease severity. (Zhou 2009).

In summary, tear and epithelial surface cell biomarkers are altered in DED but do not appear to discriminate between different forms of DED. Biomarkers are potentially attractive to track the severity of pathological events in dry eye disease and correlations with symptom levels are of interest. Recent approaches designed to generate panels of biomarkers are of diagnostic promise and may provide candidates for co-primary endpoints in clinical trials of DED.

Analysis of CIC samples provides an instant statement of the condition of the ocular surface. Tear samples are subject to the influence of reflex tearing and surface contamination. There is a need to develop small volume tear analysis methods. Sensitivity and specificity measurements should be developed in multiple populations comparing dry eye groups defined by tight criteria with normal subjects, and patients with non-dry eye ocular surface diseases.

Industry View: Auli Ropo
Ophthalmologist and head of clinical development in Europe, Santen

From a patient perspective, there should be an improvement in symptoms, a reduced frequency of eye drop instillation and an increased quality of life. From the industry perspective, safety and efficacy of treatment should be demonstrated and there should be an improvement of signs and/or symptoms. Evaluating symptoms is difficult since various symptoms are used in different studies, patients use different terminologies and symptoms associated with DED are not specific. Symptoms vary over time and are affected by external factors. The capture of symptoms also varies (e.g. VAS, validated questionnaire) and we need to decide whether to evaluate a mean or sum of all symptoms or the worst. We have to define a clinically relevant change and we don't know what this change is.

For signs, what are the signs to be used as inclusion criteria and what is a clinically significant change? Different studies have been used different signs. Some are established, for example corneal staining that has defined scales. For TBUT and Schirmer, variability can be high and repeatability is a problem. With regards to tear osmolarity, the cut off value to distinguish between normal and DED subjects is not clarified for use in clinical studies. This test is also not standard procedure and at many sites, test equipment is not available. There is a poor correlation between signs and symptoms and the development of new pharmaceutical therapies is hampered by the lack of objective tests for response outcomes.

In terms of primary efficacy endpoint(s), the industry would like to get acceptance for use of a sign only or a symptom only which is currently not the case although from a patient perspective, symptoms are of major importance. It is not clear if outcomes should be presented as responder analyses or based on mean values. For endpoints addressing inflammation, there are currently no validated tools and these endpoints are used as secondary or exploratory endpoints. Consequently, there is a need to investigate how changes in biomarkers correlate with changes in signs and symptoms and to define clinically significant changes.

Potential populations targeted in clinical studies can be categorised by severity, however it is challenging to show effect, especially on signs, in patients with mild disease. Severe patients often have concomitant disease and medications that may induce bias. In case of a decreased corneal sensitivity in severe patients, the potentially hampered evaluation of symptoms must be considered. Patients may also be segmented by their background, e.g. inflammatory disease.

From an industry perspective, we are suggesting study durations of 3-6 months for efficacy and 12 months for safety, if not otherwise justified. Another issue is the comparator. Since no active comparators are available, vehicle controlled studies aiming to show superiority over vehicle are to be

performed. However, it is difficult finding a placebo that does not affect the condition, since vehicles often contain lubricating components.

Dry Eye Disease (DED) is a heterogeneous condition and both diagnosis and endpoints for clinical trials are diverse. The Industry would welcome harmonisation of the diagnosis and measures / endpoints for clinical trials where possible. Since we currently are lacking those, the best approach for the industry would be to allow some flexibility in designing the protocols and endpoints. However, these endpoints should be very well justified and could be based on the mechanism of action of the study drug. The development and acceptability of reliable biomarkers would be helpful. The clinically relevant change of symptoms is not clear. Evaluating symptoms is difficult since variability can be high and repeatability is a problem. It is not clear what are the signs to be used as inclusion criteria and what is a clinically significant change. Development of new pharmaceutical therapies is hampered by the lack of objective tests for response outcomes.

Regulatory View: Kerstin Wickström
Senior Expert Medical Products Agency, Sweden, Member of SAWP
DED is a heterogeneous condition and the trial population needs to be better defined, not only in terms of severity of signs and symptoms, but the reasons for the dry eye have to be taken into account. The duration of disease may also be considered, since it may affect corneal sensitivity and consequently evaluation of symptoms. In DED, significant differences in symptoms and signs as a co-primary endpoint are generally required. A potential option could be to show a significant effect in a sign or symptoms with a strong trend in the other. In the selection of signs, disease aetiology, mechanism of action of the compound and phase II data should be considered. For example, frequently used signs like Schirmer and TBUT would be of different importance in evaporative vs. tear deficient disease. Tear osmolarity could be a potential marker if supported with validated evidence. Also in MGD, the appearance of lid margin and gland obstruction/drop out needs to be addressed, but tools for standardised grading and evaluation are not available. DED is a symptomatic disease and symptoms need to improve. A composite measure of symptoms is recommended, but as for signs, in MGD, no specific questionnaires are available and we don't know the overlap in symptoms compared to tear deficient dry eye. The use of one single worst symptom is discouraged since its subjectivity and variability limit usefulness as being an adequate marker of a clinical benefit. Other symptoms may also not parallel the worst baseline symptom over time.

To address the intended mode of action of the compound, markers of, for example, tear production, mucin secretion or meibum composition should be considered as secondary or exploratory endpoints. The effect has to be clinically meaningful and supported for the selected endpoint. Guidance of the size of a clinically relevant effect should come from the clinical community. We recommend that both evaluation of mean changes and responder analyses are included.

As comparator, the use of vehicle is straight forward and addresses potential effects or intolerance of the vehicle as such. Lubricants could also be acceptable if the target population are regular users, or if the composition of vehicle similar to that of artificial tears. In MGD, the choice of comparator needs to be further evaluated. Concomitant use of artificial tears may be necessary to prevent a large drop-out in case of an infrequent administration. Its use must be documented and addressed in a secondary endpoint. The duration of studies should be sufficient to confirm maintenance of effect and 6 months is recommended for primary evaluation of efficacy. For safety, 12 months is generally sufficient.

Evaluation of efficacy after exposure to a controlled adverse environment (CAE) could be useful during early development to get a proof of concept, to aid in dose selection and to evaluate biomarkers. A CAE trial is not acceptable as a pivotal trial without an environmental study since an enriched population, likely not representative for the target population, is selected. The real life heterogeneity is also lost which leads to an overestimation of the statistical effect, while the effect size in a real life population will not be known. Several anti-inflammatory products are in development for DED. Consequently, the anti-inflammatory effect needs to be addressed as secondary or exploratory markers. It is recommended that the duration of effect after discontinuation of such treatment is evaluated, especially if an intermittent chronic treatment is foreseen and a randomised withdrawal could be considered. Guidance for frequencies for potential re-treatment would also be obtained.

Due to the lack of active comparators, superiority trials are performed. Even if active comparators were available, superiority trials would be recommended since placebo can be used and assay sensitivity would be questioned. Two confirmatory studies, not necessarily replicates, are recommended.

We need to learn more about DED, to get a better understanding of the relevance and usefulness of different outcome measures and the strengths and weaknesses of the symptom scales and visual function quality of life questionnaires. The population to include in a clinical trial needs to be better defined taking the reasons for the dry eye into account. Tools for standardised grading and evaluation of signs and symptoms of MGD are not available, and we need to learn about the overlap in symptoms compared to tear deficient dry eye.

There is a confusion regarding criteria for selecting patients, which outcome measures that are of relevance and whether these should be different in evaporative or tear deficient DED. Currently, regulators require a co-primary endpoint evaluating a sign and symptoms (or at least one of these with strong support of the other), but there is a problem correlating signs and symptoms. Since this confusion is evident in the industry as well as among regulators, a meeting with an expert group to discuss how to handle these issues until further research is available could be useful.

Paediatric Investigation Plans

Background and Introduction

In 2007, The European Union's Paediatric Regulation established new responsibilities for the Agency in the field of paediatric medicines. These responsibilities included the establishment of a paediatric Committee (PDCO), and the determination of studies that companies must undertake on children as part of paediatric investigation plans (PIPs). In the European Union (EU), children are defined as persons from birth up to 18 years of age. Other roles of the PDCO involve establishing and regularly updating an inventory of paediatric medicine needs, and advising and supporting the development of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA).

Some experience has now been gained with PIPs for products in ophthalmology indications. Therefore this workshop aimed to bring together regulators, clinicians and industry to consider PIPs in this therapeutic area, examine priorities for unmet pharmacological needs in paediatric ophthalmology, and consider critical issues of clinical trial design and development in these indications. The choice of topics was dictated by PIPs submitted to date. The meeting started with a welcome by Daniel Brasseur, chair of PDCO. A brief background was given by Ralf Herold, Scientific Administrator, Paediatric Medicines section, EMA, on the European Paediatric Regulation. The regulation mandates that any marketing authorisation application for a new medicinal product should include either the results of studies conducted in compliance with an agreed Paediatric Investigation Plan or an EMA decision on a waiver or on a deferral.

As a *General approach, clinical academics* were asked to present the view from the clinic/patient covering such angles where relevant as frequency/ morbidity, natural history, current standard of care, first line/second line/third line, evidence base, threshold for treatment (if any/ threshold for withdrawing treatment/retreatment), meaningful differences with treatment, definition of refractory/response /emerging therapies/possible biomarkers, unmet needs, possibility of extrapolating adult PK and or efficacy data to children, optimal trial design and endpoints (surrogate or other-wise), need for, and feasibility of trials in view of paediatric prevalence, and appropriate age subsets. Thorsten Olski, Richard Vesely, (Paediatric co-ordinators, Paediatric medicines, EMA) Brian Aylward, Karl-Heinz Huemer ((alt) members of PDCO) briefly presented the *regulatory perspective* in relation to specific questions and problematic areas based on past experience on previous ophthalmological products. The experts were asked to also comment on specific questions sent out in preparation of the meeting.

Jugnoo Rahi , Institute of Child Health / Great Ormond Street Hospital UK presented an overview on *childhood blindness* covering the main points on the nature and quality of existing evidence on incidence and prevalence of visual impairment in children. Professor Rahi addressed the epidemiology of paediatric ophthalmological disease conditions pointing out the need for better disease-specific and more recent population based data. She gave an overview over recent attempts to gather better epidemiological data. The preventability of several of these disorders was stressed and the lack of information on long-term outcomes was pointed out.

Uveitis

Clive Edelstein (Consultant Ophthalmologist, The Ipswich Hospital NHS Trust, Great Ormond Street Hospital) introduced the topic of *uveitis*. The chronicity of uveitis and the consequent disease burden especially for children was stressed with an initially painless presentation at a severe stage rendering the diagnosis difficult. There is a potential lifelong treatment need. In this context, it was underscored

that uveitis, as a major paediatric cause of acquired blindness, was underestimated as the visual impairment/loss may manifest at a later age. There is a paucity of trials of licensed medications in uveitis in adults, and even more so in children. There is no uniformly accepted stand of care, and a lack of information on differences of prescription practice, with variation between regions acknowledged. There is a clear unmet need regarding licensed immunosuppressants products in children; estimates were presented that 1/3 of uveitis patients requiring immunosuppressant therapy are children owing to the chronicity of the paediatric entity, and the particular needs of the paediatric population in minimising steroid use.

Questions had been addressed to the clinical experts:

What are the extrapolation possibilities for treatment efficacy from adults in paediatric uveitis? The workshop discussion is summarised as follows.

Extrapolation of clinical results from adults to children was not supported, in general. Childhood patterns of uveitis differ from those in adults in terms of aetiology, clinical course, severity at presentation, and long term need for immunosuppression. The feasibility of paediatric studies found agreement. Extrapolation to the HLA-B27-positive group from adults to children was supported as entities with a similar clinical behaviour. Posterior Uveitis in children stemming from Toxoplasmosis, may be amenable to extrapolation from adults. For intermediate uveitis, extrapolation from adults was not supported, as in children, this runs a more aggressive course. Other types of Posterior Uveitis in children are not well studied, and very rare, although Behçet's disease in children may respond similarly to some agents as adults.

Alternative treatments (steroids) are prone to more undesirable effects in children, both systemically and locally with potential life-long consequences. Recommendations for simultaneous treatment in children are different. Longer time spans for follow-up are necessary for children as exemplified by the experience with previously used immunosuppressants. Furthermore, the forms of arthritis associated with uveitis are different in adults and children.

A previous rheumatology expert meeting concluded that uveitis should be studied within JIA PIPs especially for new biologics. Do you agree that patients with active JIA uveitis are included in the JIA trial?: Is the dosage expected same as for treatment of arthritis or different? The workshop discussion is summarised as follows.

An open question remains the inclusion of JIA associated uveitis patients in JIA-trials or the conduct of separate JIA-trials. Association of the two disorders, and rarity of uveitis supporting the former, but a possibly different dosing or response supporting the latter. Efficacy in JIA would not necessarily imply efficacy in uveitis. In addition, uveitic inflammatory activity does not parallel joint inflammation with 25% of cases of associated uveitis in children presenting prior to joint involvement. There are thus major differences between JIA and the associated uveitis, reflected by this difference in timing.

It was suggested to stratify in JIA by joint activity and uveitis, and not by adult /children. For non JIA uveitis, stratification in trials by severity and region (local prescribing practice) may be a way forward. Although a large number of uveitis cases in children are JIA-associated, investigating all paediatric uveitis entities in the same trial could prove problematic. Differences between intermediate uveitis, multifocal choroiditis and JIA-associated uveitis were noted. The role of conventional immunosuppressants and biological agents, and switching strategies may be different in children with implications for trial design, inclusion and rescue criteria (e.g. for second line biological modifiers, a suggestion was a placebo controlled add- on to conventional immunosuppressants, in patients who are refractory, poorly responsive or intolerant to first line immunosupressants, with withdrawal of patients from the trial with deterioration or persistence after three months). Randomised placebo controlled withdrawal designs were debated; concern was raised that the natural history of uveitis was unknown which could undermine this design. Patients with JIA-like uveitis or chronic anterior ANA-positive uveitis without any systemic symptoms were suggested to be enrolled in trials as if they had JIA associated uveitis, these as are treated akin to children with JIA associated uveitis and have a similar aggressive clinical course and responsiveness.

What are the recommended outcome criteria for paediatric uveitis? There is an absence of consensus. Are they validated? The workshop discussion is summarised as follows.
The best outcome measures are still debated for uveitis. An approach tailored to children is needed. The SUN-criteria were debated, acknowledging that the clinical relevance of outcome parameters like change in A/C cells (not been validated yet) and flare (possibly promising a high correlation to the outcome (using Laser-Flare-Photometer) were questioned in terms of prognostic value. Change in

visual acuity, and reduction in concomitant steroid were of acknowledged benefit. The potential for amblyopia was raised. Quality of life was also discussed. The relevance of measuring remission of uveitis was acknowledged. Measuring uveitis relapse rates over 2-3 years instead of time to relapse was suggested. Clinically significant rates of relapse, or lengths of remission need to be established. The measurement of visual acuity, or the use objective imaging modalities in children however, were judged to be challenging.

Anterior Segment Disorders

Jane Ashworth (Consultant Paediatric Ophthalmologist, Manchester Royal Eye Hospital, UK) gave an overview of the *conditions of the anterior segment.*

Atopic keratoconjunctivitis and vernal keratoconjunctivitis have been designated as separate orphan conditions: Is it supported to consider them as distinct entities? Is there a global consensus on the differential diagnosis of both conditions? Are there significant geographic variation in their absolute and relative prevalence in different paediatric age groups (e.g. frequent AKC in young children in Japan)? Are active-controlled trials necessary in vernal keratoconjunctivitis or could a placebo-control be accepted and how feasible would trials be in view of paediatric prevalence in the age group below 8 years? What would be the optimal time point of efficacy evaluation and which endpoints would be considered relevant? The workshop discussion is summarised as follows.

The differences between vernal and atopic keratoconjunctivitis were acknowledged supporting a separate approach to each condition with different clinical features and courses, and therefore likely different needs/responses for treatments, despite an overlap in disease mechanisms (Immune mediated ocular surface inflammatory conditions) . Clinical features distinguish these conditions.

Vernal keratoconjunctivits manifests seasonal exacerbations, affects boys more frequently than girls and resolves by puberty. Complications of Vernal Keratoconjunctivitis in children include Loss of vision, Corneal scarring, Keratoconus, Limbal stem cell deficiency, Steroid induced cataracts and glaucoma, and Behavioural/psychological impacts consequent to severe photophobia and ocular itching. Some geographical variation is apparent.

In this context, it was also underscored that the study populations for future studies should be more homogenous with more objective inclusion criteria (proposed severity grading system according to Bonini et al.). It was considered that for vernal keratoconjunctivitis, large active/standard of care-controlled multicentre clinical trials were indeed feasible and could be requested in particular in view of the long-term irreversible sequelae making placebo/vehicle controlled trials problematic. The use of steroids is well established although a uniformly accepted defined standard of care is not available, and limited licensed therapies are available for children in this indication.

The need for more standardised presentation of study outcomes was stressed. For example, the use of recurrence rates according to the previously used Oxford scale was supported as a useful endpoint. Neovascularisation was suggested as an additional potentially valuable secondary endpoint. It was pointed out that visual acuity as a secondary endpoint had to be regarded with caution in view of poor feasibility of measurement, and amblyopia. Further efficacy endpoints were suggested- corneal scarring/vascularisation, - recurrence rate (defined as 100% increase in hyperaemia, itching, Trantas dots, Oxford fluorescein and epitheliopathy score), -Symptoms score-(itching, photophobia, redness, tearing, secretion and blurry vision (graded 0-3)), - signs score (conjunctival hyperaemia, mucous discharge, tarsal and/or limbal papillae) according to Lambiase et al. A combined symptom score was suggested (itching, photophobia, redness, tearing, secretion and blurry vision). A Quality of Life (symptoms and daily activities-QUICK score) is also available.

The study duration for an investigation of vernal keratoconjunctivitis would have to be of an adequately long duration covering the incidence of typically occurring complications, e.g. recurrences, scarring, other epithelial defects, visual impairment, itching, photophobia.

Well-designed studies also in atopic conjunctivitis were considered necessary, this being a seasonal and perennial allergic conjunctivitis, which occurs in adults and children, males and females, many with a strong clinical history of atopy and eczema. There is a spectrum of severity from mild to severe with corneal scarring. The poor quality of published trials was highlighted (Lack of objective inclusion criteria, Lack of quantifiable primary outcomes, Lacking evaluation of efficacy and safety, Disease relapses and recurrence rates omitted, and Short term outcomes only). However for atopic conjunctivitis, more room for extrapolation from adults was acknowledged.

The off label use of ciclosporin, (both) and tacrolimus (VKC) in these indications was stated.

In addition to the discussion on atopic and vernal keratoconjunctivitis a medical need in paediatrics for the treatment of *blepharoconjunctivitis* was raised with appropriate randomised controlled trials still missing. Disease definition and classification is needed. These randomised controlled trials would have to establish the role of antibiotics (topical/systemic) and steroids, dose and duration of treatment, establish recurrence rates, the possibility to reduce steroid or antibiotic treatment, the extent of scarring, vascularisation, the quality of life, visual acuity as well as long-term sequelae such as amblyopia and corneal scarring.

On the topic of *inflammation control and analgesia post cataract surgery* questions had been addressed to the experts prior to the meeting:

In view of the use of general anaesthesia in cataract surgery, would there be a paediatric need for local anaesthetic products, and would it still be of benefit to include adolescents into adult trials? The workshop discussion is summarised as follows.
Incidence of paediatric cataract is estimated to be 3.5 per 10,000 by age 15 years. Cataract surgery in children and adolescents is still conducted under general anaesthesia. Peri-operative local pain control was considered to be of less relevance in the paediatric setting. For pain management, i.v. paracetamol, i.v. fentanyl, topical anaesthesia, and subtenons local anaesthaesia are known to be used peri-operatively. NSAIDS and paracetmol were prescribed as required post operatively. A greater clinical paediatric need for local pain relief was stated in the context of strabismus surgery. Potential endpoints include: Frequency of emergence agitation, Visual analogue scale pain scores, Supplemental analgesia requirement, Patient satisfaction, Wong-Baker pain scores and FLACC (face legs arms cry consolability).

Prevention of inflammation particularly needs to be addressed following paediatric cataract surgery with higher levels of inflammation seem compared to adults. The potential consequences of uncontrolled inflammation include capsular fibrosis, glaucoma, pupil phimosis, and membrane formation, especially in younger children, possibly requiring further surgical interventions. The use of plasminogen activator, heparin (applied intracamerally) and steroids applied topically, subconjunctivally or to the orbital floor was raised. The use of oral steroids was controversial. The evidence base for the optimum strategy for is limited. Variation in prescribing is acknowledged.

For the topic of *prevention of corneal graft rejection* some questions had been addressed to the experts before the meeting:

Previously, suggestions have been made by applicants to accept neovascularisation as a surrogate for prevention of corneal graft rejection. Would this be supported? To which extent could extrapolation from adult trials be possible? Would clinical studies in prepubertal children be necessary and considered feasible in view of the prevalence of keratoplasty, the fraction of paediatric patients, and the fraction of high risk patients? Would a comparison to placebo/vehicle be appropriate and what would be the preferred efficacy endpoint measurement? Do you see a paediatric need in addition to corticosteroids for more potent immunosuppressant agents in the treatment of paediatric patients, e.g. ciclosporin, in particular in high-risk patients? As a consequence, would you see a need for paediatric trials covering safety, tolerability, and efficacy? The workshop discussion is summarised as follows.

It was acknowledged that neovascularisation as a surrogate endpoint for corneal graft rejection was yet to be accepted. Treatment of corneal neovascularisation prior to corneal graft may reduce the risk of rejection but does not eliminate it.

Efficacy was deemed extrapolatable from adults to children only to a very limited extent. The clinical circumstances for corneal transplant were judged to be significantly different between adults and children with developmental abnormalities, and severe corneal dystrophies being the leading reason for transplants in very small and small children respectively. Older children may suffer keratoconus and corneal scarring secondary to infection or trauma. Furthermore, tissue healing and inflammatory reactions in very young and young children are very different with the side effect profile and the response to treatment deemed very different between adult and child populations. For example, suture removal is carried out early to avoid precipitating rejection episodes. Paediatric clinical trials would therefore still be necessary, although the numbers of patients available would be very low, with numbers of procedures peaking in those less than 1 year of age and in those 15-17 years of age.

Comparative studies would have to be conducted as add-on to steroids. It was agreed that the role of ciclosporin A as a treatment alternative to corticosteroids was to be seen critically. The argument was raised that some data may even suggest an increase in graft rejections after ciclosporin A in adults, although the particular paediatric context also needs to be taken into account. Trials would need to be adequate duration, and separate age groups would need to be examined.

Among the relevant endpoints identified were number and severity of rejection episodes, corneal vascularisation, corneal thickness (possible surrogate measure of graft rejection), visual acuity (amblyopia treatment compliance, refractive error/astigmatism) and graft clarity (iris visibility, but also new imaging techniques offer possibilities of objective measures).

For the topic of *Limbal stem cell transplantation* some questions had been addressed to the experts before the meeting:
Is there a sufficient rationale for extrapolation of efficacy results from adult studies to children? Do you see a need to verify the feasibility and tolerability of the procedure/treatment on children and given the low prevalence to which extent would you consider clinical investigations in children feasible? The workshop discussion is summarised as follows.

There is a limited rationale for extrapolation from adults to children. However, there are very few indications in children, possible with severe chemical injury or Stevens-Johnson and numbers will be low.

Glaucoma

John Brookes (Consultant Ophthalmologist, Moorfields Eye Hospital, UK) presented an expert view in paediatric *glaucoma*. It was acknowledged that the large variety of childhood glaucomas, the rarity (between 1/30,000 and 1/10,000 live births) and the variety of available medicines renders studies difficult. Despite the low incidence, the disease burden is significant in view of the long disease course and intensiveness of treatment, (currently being incurable requiring life-long treatment) and potential for vision loss.

Questions had been addressed to the clinical experts, before the meeting:
1) How far can one extrapolate adult efficacy and safety data, taking into account the developmental state of both the eye, and the body in general at the various ages? for very young children? The workshop discussion is summarised as follows.

It was agreed that extrapolation would be possible to a limited extent. Safety and efficacy would have to be demonstrated in children. Although extrapolation was considered as an option in principle for adolescents, the age group from birth to less than 3 years of age was considered to react significantly differently supported by different PK results, thus excluding extrapolation for that group. Adverse reactions from systemic absorption may be more pronounced with children. As the growth of a child's eye is nearly complete by 3 years of age, adult doses may be appropriate to achieve therapeutic ocular concentrations in children.

The need for more solid clinical data in rare secondary forms of glaucoma was underscored.

2) For the majority, medical products are used as short term adjuncts for surgery. Nonetheless, long term use can be expected in patients with secondary glaucoma, or those not amenable to surgical treatment. How does the long-term safety profile of the various agents affect patient acceptability? 3) The safety profile of timolol was improved by the introduction of a gel formulation. Could this be extended to other products to improve their profiles? The workshop discussion is summarised as follows.

Long term tolerability is of utmost importance in glaucoma, and a key to treatment success. In the majority of cases, the long term safety profile is accepted by both the patient and their families. In practice, ocular discomfort on instilling the drops is the most frequent complaint by patients, necessitating a change in the medication. A compound with acidic pH for example is often not well tolerated by children. Either changing to a preservative-free preparation, or changing to another compound, which has a more neutral pH can reduce the frequency of stinging and is better tolerated by patients. Other common examples of adverse effects of long-term use of drops are with conjunctival hyperaemia, and periorbital pigmentation caused by prostaglandin analogues.

With regards to patient compliance, it was stated that once patients were receiving a medicinal product successfully, the willingness of switching between different drugs would be less.

Although gel formulations have the advantage of reducing systemic exposure and therefore reducing the risk of adverse effects, this is often negated by the practicalities of administering the medication in young children. In practice, parents have difficulty in getting the medication into the eye and they often wish to revert back to using a drop formulation, which is easier to administer.

3) The Paediatric Regulation states the new medicinal products or forms must demonstrate a significant therapeutic benefit over existing licensed products. Where, in your opinion, would such a significant benefit lie? The workshop discussion is summarised as follows.
There is a poor evidence base for most ocular hypotensive agents used in its treatment. Surgery as primary therapy was stressed. Medical therapy is both a temporising measure, and later as topical adjunctive treatment.

The two significant benefits of new medications over existing licensed products would be superior IOP-lowering effects and lower rate of adverse effects. Glaucoma in children is an IOP-dependent disease, so the therapeutic priority is having a product that reduces IOP more successfully than other products, in a way which is easy and acceptable to use for the families having to instill the drops. The other benefit would be to try and have a product which has to be instilled as infrequently as possible, perhaps by having a sustained release agent.

4) The ideal trial design to demonstrate the efficacy of these products is believed to be a 3-arm, blinded, placebo and comparator controlled trial, with group numbers weighted toward the active arms. In addition, such a trial might have a 12 week treatment period, depending on the test and comparator substances. Given the prevalence and incidence of these conditions, can you comment on the feasibility of such trials? The workshop discussion is summarised as follows.

The issues with trials in this group of patients include: 1) the relative rarity of the condition, especially in secondary glaucomas, 2) the clinical variability between cases, 3) the likelihood that the disease could progress within the trial period, as glaucoma in childhood is often a more aggressive disease and can result in deterioration at a faster rate than glaucoma in adults.

The various subtypes of paediatric glaucoma were considered to be so rare that separate studies could not be considered feasible. Basic criteria for distinction of different forms would rather have to be applied for later analysis. In view of this rarity of the disease, a separation of only the most important disease subgroups, primary congenital and aphakic glaucoma, was supported with a separation below and above 3 years. The relevance of safety data for the age group below 6 months was stressed.

Taking the example of the first prostaglandin analogue to be authorised as monotherapy in children, latanoprost, aspects of clinical trial design were elaborated on. The mean change in IOP at week 12 was supported as a primary endpoint. Responder rates identified at week 4 and 12 were very considered very valuable. With better responder rates expected in secondary glaucomas, the need for more efficacy data in that population was stressed, in addition to evaluation in primary congenital glaucoma.

Retinopathy of prematurity

Gill Adams (Consultant Ophthalmologist, Moorfields Eye Hospital UK) elaborated on the clinical presentation, epidemiology, clinical course of retinopathy of prematurity, long-term sequelae, classification. The workshop discussion is summarised as follows.

Regional differences were pointed out. ROP in developed countries is now mainly a disease of micro premature babies with a birth weight <800g, < 26 weeks gestation at birth and is a ppotentially blinding disease. The importance of early screening and early and immediate treatment was underscored. Country specific guidelines are in place appropriate to local conditions. Despite a good evidence base for treatment, long term visual outcomes are in the range of 44% with an acuity of $\leq$20/200. Practical problems of rapid surgical intervention/laser were laid out. The need for new treatment options also stems from the resources need for laser intervention, i.e. need for training and use of personnel resources, as well as the clinical consequence of peripheral field defects after laser treatment. Anti-VEGF agents were thought to offer a potentially cheaper and quicker primary treatment option in ROP. The potential ocular and systemic complications are highlighted. Anti-VEGF agents are being used off label in ROP.

The BEAT-ROP study is the only randomised controlled trial for ROP with anti-VEGF in children. Interestingly, differences in clinical outcome between zone 1 and 2 disease were detected differing from the outcome for laser treatment (zone 2 disease better with laser in contrast to zone 1). The discussion pointed out the general difficulty of demonstrating safety in a long-term follow-up, and practical problems when examining the peripheral retina to exclude the late peripheral retinal recurrences in an outpatient setting which appears to occur with Anti-VEGF treatment. Specifically, the high failure rate with laser in the BEAT-ROP study was brought up to question the trial quality and external validity. Possible systemic absorption of intravitreal agents with systemic VEGF-suppression was raised as a safety concern, with potential for effects on VEGF-dependent development, and pulmonary hypertension. An appropriate dose-determination was considered indispensable. As a practical problem for the conduct of studies, the appropriate determination of developmental problems that are the result of prematurity was raised.

Further trials are needed in this indication with anti-VEGF agents to establish safety and efficacy in ROP. The need for collaborative efforts from regulators, academia and industry to promote investigations into this condition was acknowledged. Design trial parameters should be agreed with regulators prior to start of the trial. The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA), and the European Paediatric Ophthalmological Society were flagged as relevant potential collaborative partners.