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Regulatory workshop on clinical trials designs in neuromyelitis optica spectrum disorders (NMOSD)

Report of EMA workshop 10 October 2014 London

Summary

Scientific advice at an EU level may be requested for all medicinal products for use in humans on aspects of the design of studies, trials and programs to support quality, safety and efficacy of a medicinal product at EU marketing authorisation. In the context of a rare disease with a significant unmet medical need, a limited population necessitating a global development and apparent different regulatory viewpoints, it was seemly that a wider debate was held on the topic of trial designs to facilitate global new drug development for the benefit of NMOSD patients. The workshop was held at the EMA on the 10 October 2014 with sessions on disease diagnostic criteria, epidemiology and natural history, the evidence (or lack thereof) for currently used treatments in NMOSD, considerations for placebo and nonplacebo-controlled trials, endpoints and paediatric aspects of drug development. Clinical, industry, regulatory, ethicist and patient views were presented. Presentations and videos of the workshop are available [here](#).

Further to discussions at and after the above mentioned workshop, EU regulators (the scientific advice working party and committee for medicinal products for human use) have made the following reflections with regard to the question of placebo controlled trials in relapse prevention in NMOSD. Randomised placebo add-on controlled or active controlled trials for experimental treatments are strongly preferred in trials for relapse prevention in NMOSD according to upcoming revised criteria. Testing for superiority is expected. However, consideration of the status of the evidence of current standard of care, and design options for potential placebo only controlled trial options in NMOSD leaves room that a randomised placebo only controlled trial versus experimental treatment in the above patient populations may be an acceptable choice for some clinicians and some patients. All legal, ethical and regulatory requirements for such studies must be fulfilled, whether studies have been conducted within or outside the EU/EEA. The likely risk and nature of a relapse to the individual patient in all these trial options must be considered and comprehensively explained as part of a fully informed consent procedure. Further details and caveats of different trial options are discussed below. A randomised placebo controlled trial would be acceptable in NMOSD patients who have failed or who are intolerant to previous treatments. Further reflections on other selected NMOSD clinical trial design issues are also highlighted from the Workshop. Seeking product-specific EU scientific advice is recommended.



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1. Post-workshop regulatory report

1.1. Background

Role of EU regulators in drug development

Scientific advice at the European Union (EU) level may be requested for all medicinal products for use in humans on aspects of the design of studies, trials and programs to support quality, safety and efficacy of a medicinal product at marketing authorisation in the EU. The scientific advice working party (SAWP) is a standing working party of the committee for medicinal products for human use (CHMP¹) with the sole remit of providing scientific advice and protocol assistance (the name given to the scientific advice procedure for products with an orphan designation) to applicants.

According to the published mandate of the SAWP (EMA/CHMP/SAWP/69686/04 Rev 9), "...the SAWP will need to reflect on potential ethical issues associated with different possible trial designs, both for those submitted by applicants and for alternatives considered during discussions when ensuring that all advice given is scientifically, clinically and ethically sound. However, this position shall not substitute for the opinion of appropriate ethics committees". All clinical trials, conducted within the European Community, must comply with the requirements of directive 2001/20/EC of the European parliament and of the council on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Ethical considerations of studies

Clinical trials conducted outside the EEA have to comply with ethical principles equivalent to those set out in the EEA, including adhering to international good clinical practice² and the Declaration of Helsinki. According to the Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities "During the course of the MAA assessment, any relevant ethical issues such as access to treatment post trial, use of placebo or treatment interruptions, choice of active comparators, treatment of vulnerable populations should be highlighted as part of the assessment of the individual trial. The justifications for the study designs, choice of comparators and selection of study populations should be provided with particular emphasis on those studies that involve increased ethical sensitivity due to their design, indication, patient population or location of conduct. The applicability of the trial to the EEA population should be discussed where relevant." If the CHMP concludes that a study has not been carried out in accordance with the appropriate ethical requirements, the CHMP must conclude upon additional steps, which could involve excluding data from the studies or part of the studies deemed unethical.

Applicable guidance including small populations

In preparing its integrated advice on a proposed drug development program, the SAWP takes into account the scientific standards as required in directive 2001/83/EC of the European parliament and of the council as amended, and all applicable CHMP guidelines to ensure the best possible approach has been taken. SAWP will ensure that proposed studies are also in line with internationally accepted principles and practices in the conduct of both individual clinical trials and overall development strategy for new medicinal products, including the protection of clinical trial subjects and a scientific approach to design and analysis. The CHMP guidance on small populations (CHMP/EWP/83561/2005) acknowledges problems associated with clinical trials when there are limited numbers of patients available to study, owing to the rarity of the condition.

¹CHMP is the committee at the European Medicines Agency that is responsible for preparing opinions on questions concerning medicines for human use.

Reason for workshop

Neuromyelitis optica (NMO) or Devic's disease is a rare inflammatory and demyelinating autoimmune disorder of the central nervous system (CNS) characterised by recurrent attacks of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM). NMO was traditionally restricted to the optic nerves and the spinal cord but now a unified and broader disease categorisation called NMO spectrum Disorders (NMOSD) is now considered applicable. In this report, where appropriate, the term NMOSD is adopted to encompass NMO and associated spectrum disorders as guided by upcoming revised criteria. There are no approved therapies. In Europe for NMOSD, long-term treatment for relapse prevention although unapproved, is offered as soon as the diagnosis of NMOSD is made as the prevention of attacks is the key issue for reducing permanent disability. Approval of new medicines for relapse prevention in NMOSD necessitates submission of evidence demonstrating a favourable risk benefit balance in the target population for that product, based on randomised controlled trials. In NMOSD, the choice of control appeared to be problematic. The rarity of the disease, severity and lack of reversibility of the relapses, early morbidity and mortality in untreated NMOSD, suggested that placebo-controlled trials were difficult [Jacob et al. J Neurol Neurosurg Psychiatry 2013;84:922–930], yet the evidence supporting the use of current treatments appears lacking. Compounding this, different regulatory agencies had taken different standpoints on the appropriate choice of comparator for the robust determination of safety and efficacy in new products intended for NMOSD attack prevention. In the context of a rare disease with a significant unmet medical need, and a limited population necessitating a global development, it was seemingly that a wider debate was held on this topic to facilitate global new drug development for the benefit of NMOSD patients in this rare disease.

1.2. Workshop Outline

The workshop was held at the EMA on the 10 October 2014 with sessions:

- on disease diagnostic criteria, epidemiology and natural history,
- on the evidence (or lack thereof) for currently used treatments in NMOSD,
- considerations for placebo controlled trials, including possible measures to mitigate risk to trial subjects in a placebo only arm,
- possible non placebo controlled trials
- endpoints
- paediatric aspects of drug development

Clinical, industry, regulatory, ethicist and patient views were presented.

Further details of individual presentations are summarised in Section 2 of this report. Presentations and videos of the workshop are available [here](#).

1.3. SAWP and CHMP post-workshop reflection on placebo controlled studies in NMOSD

Further to discussions at and after the above mentioned workshop, SAWP and CHMP have made the following reflections with regard to the question of placebo controlled trials in relapse prevention in NMOSD.

It should be noted that these reflections do not constitute comprehensive scientific guidance, or replace product-specific EU scientific advice which would be tailored to specific development plans.

The EU regulatory position post workshop is that:

Randomised placebo add-on controlled or active controlled trials for experimental treatments are strongly preferred in trials for relapse prevention in NMOSD, when considering the recruitment of NMOSD patients according to upcoming revised criteria (encompassing NMO or NMOSD AQP4-IgG² positive or AQP4-IgG negative patients conforming to the criteria), who are apparently responding to immunosuppressant therapy. Testing for superiority is expected.

² Autoantibodies associated with NMOSD and subsequently identified as binding to Aquaporin-4 (AQP4); thus patients can be identified as antibody (NMOSD AQP4-IgG) positive or negative.

Where a design testing for superiority of the experiment therapy to an *active comparator* is planned, efforts should be made to contextualise the effects seen. It should be substantiated that the active comparator chosen has not shown any indication of being harmful. If there is no strong reason to expect the new drug to be at least as good as the currently used therapy, an add-on study may be more appropriate. Regarding add-on studies in NMOSD relapse prevention, efficacy is established by such studies only for the combination treatment, and the dose in a monotherapy situation might be different from the dose found to be effective in combination. However, adequate exploration of combination subgroups should be assessed in the add-on setting. Subsequent withdrawal of background therapy in the experimental arm may be considered where justifiable and could provide supportive information on monotherapy.

However, consideration of the status of the evidence of current standard of care, and design options for potential placebo only controlled trial options in NMOSD leaves room that a randomised placebo only controlled trial versus experimental treatment in the above patient populations may be an acceptable choice for some clinicians and some patients. EMA/CHMP would not reject such studies submitted to the EMA in support of a Marketing Authorisation on the basis of this point but all legal, ethical and regulatory requirements for such studies must be fulfilled, whether studies have been conducted within or outside the EU/EEA. Whilst it is acknowledged that in an active controlled superiority trial, the expected difference between two drugs is potentially smaller than the expected difference between test drug and placebo, leading to larger sample sizes for active controlled studies, the likely risk and nature of a relapse to the individual patient in all these trial options must be considered and comprehensively explained as part of a fully informed consent procedure.

For all trials, the applicability of the trial to the EU/EEA population should be considered and discussed at the time of submission, given the ethnic or other factors which may influence clinical outcome or response to treatment. For example, it should also be examined whether the placebo controlled study has recruited less ill or lower risk subjects than might have been enrolled in an active controlled or add-on study. The representativeness for the overall NMO population, patterns in missing data, and impact of a limited number of participating centres should be reviewed carefully. In addition, for the risk benefit assessment, the therapeutic effect size seen must be placed in context of responses seen with currently used therapies. (EMA/759784/2010, EMEA/119319/04, EMEA/119319/04).

A randomised placebo controlled trial would be acceptable in NMOSD patients who have failed or who are intolerant to previous treatments. Patients could be maintained on existing immunosuppressant therapies where possible. The definitions of failed or intolerant remains to be constituted but should be specified carefully prior to trial start.

1.4. Reflections on other selected NMOSD clinical trial design issues highlighted from the workshop

New diagnostic criteria

A revision of the diagnostic criteria are upcoming with a unified term of NMOSD encompassing NMO and SD stratified as Aquaporin-4 (AQP4) IgG positive or negative if satisfying the new proposed criteria. There may be considerations for marketing authorisation indications if pivotal clinical trial populations have been restricted. Ultimately, the indication granted would reflect the trial population. For a broader indication wording, evidence based justification for extrapolation beyond the immediate trial population would need to be submitted. Important prognostic subgroups should be pre-specified for analysis.

Primary endpoints: time to relapse (TTR) vs annualised relapse rates (ARR)

A time to relapse event is considered acceptable as primary endpoint. Nevertheless, there should be exploration and discussion of limitations and assumptions inherent in this approach.

Relapse diagnosis

Relapses should be evaluated and handled by the treating physician; the definition of confirmed relapse should also include confirmation by an independent examining physician (examining neurologist) who is otherwise not involved in the subject's management and care. CHMP recommends

using the investigator-confirmed attacks for the primary analyses and to conduct sensitivity analyses using the adjudicated cases. There is currently no universally agreed definition of relapse; an operational definition should be well justified and prespecified.

Secondary endpoints

Disability should be assessed as a key secondary endpoint. For disability, there is no NMOSD specific scale. Pain scales need to be considered. Quality of life should be assessed. The development of NMOSD specific disability, quality of life and patient reported outcome measures is encouraged together with paediatric versions of relevant scales.

Single study

A single pivotal study could be considered sufficient for an MAA in NMOSD, if a clinically relevant treatment effect has been demonstrated. Analyses of secondary endpoints should be supportive for the results on the primary endpoint. The acceptance of a single pivotal study from a regulatory point of view will take into consideration a number of aspects, including the internal and external validity of the study, the clinical relevance of the effects observed, the degree of statistical significance, internal consistency, and overall data quality (CPMP/EWP/2330/99), taking into account the rarity of the disease (CHMP/EWP/83561/2005.)

Safety

These data are essential and efforts should be maximised to collect adequate, informative data.

Paediatric data

Paediatric NMOSD is an orphan disease. It is hence recognised that clinical trials in children will be difficult to conduct.

Based on the similarity of the disease between children and adults, extrapolation of efficacy from adults to children could be applied. Applicants should justify their extrapolation concept and what type of supportive study(ies) will be needed. In general, paediatric dosing should be justified based on paediatric PK data. Based on the proposed extrapolation plan, different trials designs could be acceptable. Including a placebo only arm would likely make trials difficult to conduct in the EU.

Paediatric patients included in a study should be comparable (same inclusion/exclusion criteria) to the adult source population in order to allow extrapolation.

It may be possible to include adolescents in the adult studies when there are sufficient data to support that this approach is safe and the dosing has been justified.

Applicants considering development of their products in paediatric NMOSD are advised to have early interaction with EMA (SAWP/CHMP, and the paediatric committee (PDCO)), in order to seek scientific advice and protocol assistance and to agree a paediatric investigation plan where appropriate.

2. Summary of workshop sessions

The sessions summarised below reflect the views of the individual speaker

2.1. Population

J Palace, John Radcliffe Hospital Oxford Multiple Sclerosis and NeuroMyelitis Group, UK, presented a clinical view on the NMO epidemiology to set the scene and provide an insight into high level variability.

NMO is an inflammatory disease of the central nervous system with a predilection for the optic nerve (ON) and spinal cord. Autoantibodies with an NMO IgG assay were first reported by Lennon et al, Lancet 2004 and subsequently identified as binding to Aquaporin-4 (AQP4) - a water channel protein expressed in astrocytes. NMO is a worldwide disease, affecting all ages and with a female predominance. There is some variation between manifestations and susceptibility in different ethnic groups with afro-caribbeans being over represented in Europe and US. The age of onset is on average around 40 years but varies depending on ethnic group. Age of onset appears to affect outcomes with earlier onset associated with more visual morbidity and older onset age is associated with more motor disability. Assays have changed over time. Antibody assays can differ in sensitivity depending on assay technique, isoform of AQP4 used, observer, kit or laboratory. The discovery of the AQP4 antibody revealed a wider clinical phenotype referred to as NMO spectrum disorders; those with long cord lesions, certain types of ON such as recurrent simultaneous bilateral or severe, or with lesions outside the ON and spinal cord particularly affecting the brain stem and periependymal regions.

If a suspected NMO patient is AQP4-IgG negative, it should be ensured that the most sensitive assay has been used. AQP4-IgG positive NMO and AQP4-IgG positive NMOSD are considered the same disease with the vast majority starting as NMOSD. AQP4-IgG positive NMO/NMOSD is a relapsing disease with high mortality and morbidity. Relapses are the total cause of disability. AQP4-IgG negative NMO or NMOSD patients include those with many different conditions but approximately one third appear to have true relapsing NMO/NMOSD, and possibly 30% will have MS. Approximately 30% percent of AQP4-IgG negative patients are monophasic. Myelin oligodendrocyte glycoprotein (MOG) antibodies are found in AQP4 negative NMO and NMOSD patients and may often be monophasic and often with longitudinally extensive transverse myelitis and or optic neuritis. MOG antibody disease (in contrast to AQP4 antibody disease) has a male predominance and is associated with better recovery, although there are exceptions. It may also be seen in children with an ADEM or MS like picture. All AQP4-IgG positive and relapsing AQP4-IgG negative NMO/NMOSD are offered immunosuppressant therapy. The prevalence in Europe is about 1:100,000.

2.2. Natural history of neuromyelitis optica

F Paul, Department of Clinical Neuroimmunology, NeuroCure Clinical Research Centre, Charité University Medicine Berlin, Germany, presented a clinical view on the natural history of the disease to further clarify which population may be most feasible as a trial population for placebo controlled trials.

Clinical predictors of a relapsing course include age of onset, female gender, mild initial motor impairment and a longer interval between the first 2 index events. Predictors of lower survival include a history of autoimmune disease and a higher attack frequency within the first 2 years. Most studies are consistent regarding the devastating disease course in many patients resulting in 60% with severe visual loss in at least one eye. A high proportion are EDSS 6 (wheelchair bound) in 8-10 years with more rapid accrual of permanent disability than classical (15 years +) MS, even in cohorts of treated patients. Accrual of irreversible neurological disability is almost exclusively attack-related. A progressive course is rare. There are some differences apparent between AQP4-IgG positive and negative disease based on gender ratios, relapsing course, and ancillary autoimmunity diseases. Genetic factors may be important with apparent differences regarding onset, severity, relapse frequency and outcomes.

Our knowledge on disease course prognosis and survival rate is based on retrospective cohorts. These studies have methodological limitations. There are differences in ethnicity between cohorts which can

influence disease prognosis and outcome. However, mortality seems to have decreased, presumably related to earlier diagnosis and treatment, from approximately 30% mortality rates in 1999 to <10% in 2010. Overtime, there have been changes in diagnostic criteria, and with increased awareness, patients may be diagnosed or treated earlier which may have had a beneficial effect. Multiple Sclerosis medicines may be harmful or ineffective, however, there are little data on how immunosuppressants may influence disease course in long term. Factors associated with the time to next attack in NMO were examined with an accelerated failure time models with random effects (Sung-Min et al, PLOS One 2013). The time to next attack in NMO can increase naturally in the later stages of the disease, as the number of cumulative attacks increases. Nevertheless, both combined azathioprine treatment with continued oral prednisolone and rituximab treatment were also associated with a longer time to next attack, independently of the natural disease course of NMO.

Although a subset of patients may have mild disease, the concept of “benign NMO” remains elusive. Prevention of further attacks should be the major goal of long-term treatment and in clinical trials

2.3. Revision of diagnostic criteria for neuromyelitis optica

B Weinshenker, Mayo Clinic, US, presented on evolving diagnostic criteria, and potential consequences for clinical trial designs.

NMOSD should be the unified term incorporating NMO and spectrum disorders stratified by sero-status. For diagnosis, a clinical presentation is required; AQP4-IgG positivity alone is insufficient. For AQP4-IgG positive NMOSD, at least one of the six core clinical characteristics is required to make a diagnosis of NMOSD. The core clinical characteristics are: 1) optic neuritis, 2) acute myelitis, 3) area postrema syndrome e.g. nausea/vomiting/hiccups, 4) other brain stem syndrome, 5) symptomatic narcolepsy or acute diencephalic syndrome with MRI lesion(s), 6) symptomatic cerebral syndrome with MRI lesion(s). No better explanation, or clinical /MRI red flags should be apparent. Details of revised diagnostic criteria will be published including MRI lesions and clinical and laboratory red flags.

For patients who are AQP4-IgG negative (or unavailable), to make a diagnosis of NMOSD, there must be at least two core clinical characteristics one of which must be: optic neuritis, acute myelitis or area postrema syndrome. These should be disseminated in space and there must be additional MRI support. There should be a negative test(s) for AQP4-IgG using best available assay, unless testing is unavailable.

For paediatric subjects, the same criteria as adult NMOSD apply, although LETM is more common in paediatric MS and causes more difficulty in separating NMOSD and MS. There is a greater incidence of cerebral presentations in paediatric NMO. MOG antibody detection is an evolving area and potentially promising. This is not included in NMOSD diagnostic criteria.

The implications for clinical trials include the following. It is estimated to double the potential number of cases which will facilitate enrolment and enhances study feasibility. However, changes in diagnostic criteria makes using historical data on prognosis/outcome more difficult or unreliable. Also, the change will increase heterogeneity in prognosis, unless restrictions in enrollment criteria are applied.

2.4. Discussion 1

Questions from the Chair:

- The role of IgG AQP4 assays seems to be very important, what are the proposals for harmonising or for selecting the best assays with the best performance criteria?
- Do patients that enter a clinical trial have to have a confirmation of the AQP4-IgG status with a single assay prior to the trial?

A range of responses from the audience was evident:

- The cell-binding assays seem to have the best sensitivity and best specificity although performance characteristics are good for all tests. When used in a low clinical probability state, disparities are highlighted between tests with ELISA being more sensitive but also showing false positives. Other features are noted. Trend to use cell binding assays as the primary method.

- EU consortium on NMO proposing gold standard for AQP4-IgG detection which is an important step being a key marker for diagnosis. Cell based methods favoured in the EU.
- If only include AQP4-IgG positive patients, can new medicines be used in patients without confirmed AQP4-IgG positive status?
- There are potential problems when including AQP4-IgG negative patients; the group is very controversial: small separate group (~30%), clinical characteristics are non-specific, can be mimicked. These competing diagnoses would have to be screened out, but this could be handled, and patients stratified.
- Some patients start as antibody-negative and then become seropositive. Re-testing may be needed. The existence of false positive tests should also be acknowledged and therefore this clinical diagnosis for recruitment clinical trials is also important.
- All NMOSD patients should be included in the clinical trial. Adjudication committees could be used to confirm diagnosis, minimise heterogeneity, and develop medicines across whole population.
- From Industry, the more homogenous the population for a clinical trial, the better for the study. A second study could look at the seronegative patients.
- Clinical; The inclusion of relapsing AQP4-IgG negative should be considered when using relapse-based endpoint in the clinical trials.

2.5. Current standard of care - clinical view

R Marignier, Service de Neurologie A and EDMUS Co-ordinating Center, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, France, presented on a clinical view on the current standard of care (SOC) in NMO.

There is no RCT level A evidence in NMO; most studies are single-arm, open-label, with no control group, in small numbers of people, given the fact that NMO is a very rare disease and only well characterised recently (2004-2006).

The standard treatments considered in recommendations and guidelines are Azathioprine (Aza)- a DNA synthesis inhibitor, Mycophenolate Mofetil (MMF)- cytostatic on T, B lymphocytes, and Rituximab (RTX)- a chimeric monoclonal antibody against CD20.

Evidence of widespread use of this standard of care (SOC) is published for North and South America, Asia, Europe. Guidance has been provided by NeuroMyelitis Optica Study Group, (NEMOS, Germany) European Federation of Neurological Society, and Guthy Jackson Foundation (WorldWide). A standardised regimen is widely accepted for Aza, MMF and RTX. Support for use of these agents is based on the physio-pathological rationale and level of evidence in other indications.

A summary of the evidence of benefit in NMO is provided based on 10 open-label retrospective studies, where the number of patients per study > 25, the duration of follow-up > 18 months and where studies have the same endpoints. Median Annualised Relapse Rate (ARR) shows a strong downward trend from ARRS of between 3.55 and 1 before treatment to less 1 after immunosuppressant treatment, in contrast with the trend in studies of beta-interferon.

Median Kurtzke Expanded Disability Status Scale (EDSS) based on nine open-label retrospective studies, with the number of patients per study > 25 and duration of follow-up > 18 months shows a trend for EDSS to be the same or better as before treatment. For discontinuation rates, (8 studies with the number of patients > 25, duration of follow-up > 18 months) most of studies have discontinuation rates of less than 25% of patients after treatment of 1.5 years.

There is indirect evidence of changing mortality over time. This appears to be most likely an effect of treatment with a shift from interferon beta/Cyclophosphamide to AZA/MMF/RTX rather than due to the change in diagnostic criteria. An assessment of the impact of current treatments on relapse disability suggests that relapses under treatment are less severe than relapses off treatment.

NMO and NMOSD AQP4-IgG positive share the same physiopathology and it is recommended in guidelines that "For NMO or NMOSD patients with established relapsing disease, long term immunosuppression is recommended".

In summary, there are strong evidence for the use of current SoC in NMO: i) long-term experience of efficacy and safety of these treatments in other inflammatory and antibody-mediated disorders; ii) no signal of a detrimental effect for these agents in NMO patients; iii) accumulated direct and indirect evidence for efficacy and reasonable safety in NMO. However there are clinically relevant unmet needs in NMO; these are a need for a higher level of evidence for the standard of care and a need for new treatments with a more favourable benefit/harm balance than current standard of care (SOC).

2.6. Current standard of care – industry view

E Katz, MedImmune presented an industry clinician view on the level of evidence and uncertainty of the current standard of care in relapse prevention in NMO.

Immunosuppressive therapy in NMO is an empiric, unproven therapy based on the lowest level of evidence and probably should not be labelled as “standard of care”. Possible definitions of “standard of care” include those from a legal and medical perspective. From a legal perspective, standard of care is *“The caution that a reasonable person in similar circumstances would exercise in providing care to a patient.”* From the medical perspective *“consensus statements should represent views from a broad-based, nonadvocating, balanced, and objective panel of experts”* and that *“Modern and scientific healthcare should be firmly set in evidence-based medicine; the term standard of care should be used with caution.”* Regarding the published guidance, EFNS states that *“There are no randomized-controlled trials and currently only class IV evidence for effect of any medication for relapse prevention. Hence, data favouring specific therapies are weak. Immunosuppression is the preferred treatment, but optimal drug regime and treatment duration are yet to be determined.”*

A systematic review of the literature in compliance with MOOSE and PRISMA guidelines for systematic review research was commissioned. MEDLINE, Embase, and Cochrane data bases were searched. This included all publications before January 31, 2014. There were 105 accepted studies reporting results from NMO therapies in maintenance and acute treatment. The majority of published studies were small, observational studies. This review concluded that, in the absence of controlled trials, the observed downward change in ARR or EDSS may be due to treatment effect or regression toward mean and/or the selection bias of the cohort being studied. These observational studies rarely included sufficient methodology details to evaluate selection or information bias, and confounding factors. Benefit/risk assessment for maintenance therapies could not be determined due to minimal publication of safety evaluations. There are also inherent faults in existing studies, in addition to their all being retrospective case studies with no comparator. AQP4-IgG was discovered in 2004. This means that there were different patient populations before and after 2004, and non-standardised methodologies. The revised NMO diagnostic criteria published in 2006 also means that there was a different patient population before and after this time point. There is also no unified accepted definition of NMO relapse. No safety data were reported in most studies. Lastly, dose regimens and length of therapy differ largely within studies and between studies. All these studies meet class U per American academy of neurology criteria. In summary, the data on current treatments for NMO are inadequate or conflicting; given current knowledge, these treatments are unproven and the evidence base is probably not a sufficient as a basis for writing treatment guidelines.

2.7. Non placebo trial designs for NMO – industry view

W Wasiewski, Alexion, presented the pros and cons of different non-placebo controlled designs from an industry perspective.

The following designs were considered in this presentation: 1) placebo controlled add-on to current therapy, 2) active-controlled, 3) randomised withdrawal, and 4) historically controlled.

1) Placebo controlled add-on to current therapy. The experimental treatment is added-on to background therapy in both treatment arms, so no one is on placebo alone. The background treatment could be a stable maintenance dose of any empiric therapy or combination e.g. azathioprine plus steroids, OR could be a fixed dose of a single specific empiric therapy e.g. azathioprine, OR a specific empiric therapy with no dose restriction.

The advantages of this approach are that this design may reduce the risk of relapse for the “placebo” arm by allowing empiric therapy as background therapy in this group. It must be recalled that patients are still at risk for significant relapses even on background empiric therapy. There is no need to

withdraw current therapy which is helpful given that it is unclear how long the lingering effects could last. This add-on design can establish that the new treatment is better than present treatments and can define the treatment effect of empiric therapy in the placebo arm.

The disadvantages are the potential for “attribution of benefit to combined treatment”, and that it may be difficult to establish the treatment effect of the new therapy, if it is not robust. However, currently robust and transformational new treatments are needed in NMOSD. Patients may have already failed several empiric therapies; consequently patients may not wish to restart a prior failed medication if a design pre-specifies a particular background therapy. This add-on design may mean that the total number of events in the trial to show efficacy in an add-on design is greater compared to a placebo only design. It must be considered whether there are additive safety risks stemming from the combination of background plus the experimental treatment. In the efficacy assessment, certain questions need to be answered; can the effect of the new treatment be clearly defined? Is the treatment effect dependent on the presence of other treatments (i.e. only effective if any of these concomitant medications are used)? Is the treatment effect only present with one type of concomitant medication subgroups? Is there an additive treatment effect? With robust treatment effects, there will be a clear separation of groups. This can also be checked with sensitivity analyses. The sensitivity analyses should compare subgroups of empirical therapies for each empiric therapy i.e. AZA + Active vs AZA + placebo. If the treatment effect is robust, sensitivity analyses have the potential to determine if the effect is due to the combination or is independent. Group size may limit interpretation due to power considerations.

For the safety assessment, it must be asked if there is additive toxicity. Therefore, the mode of action of both treatments and off target toxicity must be considered. The risk can be mitigated by understanding the safety profile of both agents (e.g. prior usage in other indication), assessment of pharmacokinetic and pharmacodynamic interactions, enhanced safety monitoring, defining adverse events of special interest, and unblinded safety review by a data monitoring committee.

2) Active-controlled trials. A comparator study appears more problematic in this setting; why compare to an unproven therapy? A comparator must be established to be better than placebo and there is no comparator that meets these criteria in NMOSD. A superiority trial would be needed. Powering would be problematic as annualised relapse rates are not firmly established for empiric therapies. This design would only compare the experimental treatment to one treatment regimen: regional differences can restrict the ability to do global trial. Worsening caused by one therapy could be interpreted as efficacy of the other treatment.

3) Randomised withdrawal trials. In the withdrawal trial design, treatment with the experimental compound is started as add on to existing therapy. Empiric therapy is withdrawn at specified time, over a specified time interval with randomisation to experimental and placebo arms. Empiric therapy can be a stable background treatment, a prescribed stable single medication, or against combination treatments, thus requiring two types of withdrawal. The advantage is that there is a mechanism to withdraw empiric treatment in a controlled manner. The disadvantages are that it is unclear how long the effects of empiric therapy persist, and the risk of relapse in this clinical scenario is unknown, thus making it difficult to power a study.

4) Historically controlled trials. As the understanding of NMO has evolved significantly with discovery of AQP4-IgG, the time to diagnosis has shortened dramatically (12.4 years prior to 2004 to 0.1 years 2009). Also, new diagnostic criteria have been proposed several times since 1999. Some prior empiric treatments are now known to be detrimental. Therefore, defining the appropriate historical control group would be difficult to enable a fair comparison. It would be necessary to match on several characteristics (e.g. gender, race, age of onset of first attack, serotype, onset attack phenotype (i.e. type of onset attack)).

5) Placebo controlled trials. Whilst the placebo only trial appears the cleanest trial design, there are risks to the patient. The incidence of relapse in this clinical scenario is unknown and enrollment may be difficult. Mitigation strategies to reduce risk appear not adequate: these include reducing time on placebo, and a liberal escape. It is not evident that mild relapses exist. With unequal randomisation ratios, still patients will be on placebo alone and, without treatment, relapses appear worse.

In summary, the add-on study trial design offers some degree of protection against relapse to the placebo treated patients. It is recognised that the standard of care is empirical but this permits comparison to empiric therapies, not just placebo. There is no need to withdraw relapsing patients

from current therapy. If the treatment effect is robust, the therapy would be transformative. Sensitivity analyses have the potential to determine if the treatment effect is due to the combination or is independent and patients may see this option as more acceptable.

2.8. Placebo clinical trial designs for NMO

B Cree, UCSF, presented a clinical view (US) on the rationale, pros and cons for placebo controlled trial designs in NMOSD.

Case series are inadequate for determining efficacy. A decline in relapse frequency could occur independently from treatment e.g. as a consequence of natural history. In NMO, attacks often cluster, especially around the onset of the disease. "Regression to the mean" following treatment in relapsing cohort always causes over-estimation of the treatment effect. To make meaningful claims of efficacy, in general, a control group is needed, either an alternate treatment or no treatment. No parallel groups are available in the NMO case series. Treatment selection in all studies is influenced by known and unknown biases from both clinician and patient. Matching can control for known confounders but unknown confounders can only be accounted for by randomisation. Data acquisition in the majority of case series was retrospective, unblinded and subject to bias. For efficacy evaluation, well defined endpoints collected prospectively are needed (eculizumab trial was prospective). All case series in NMO have a relatively small sample size with further biases. There are notable examples of observational studies in which subsequent randomised trials did not support accepted medical beliefs, including hormone replacement therapy in postmenopausal women, mycophenolate mofetil in myasthenia gravis, embryonic substantia nigra transplantation for Parkinson's disease and Donepezil for memory impairment in MS.

There is a case for equipoise in NMO treatment. Although, there are case series providing suggestive evidence of efficacy of current treatments in NMO, proof of efficacy requires randomised controlled trials with validated endpoints.

What about using an active comparator? There are no proven treatments, therefore any comparisons made against a treatment that is actually harmful could result in assigning benefit to a treatment that had no effect and only appeared to be beneficial because the alternate treatment caused harm e.g. flecainide or encainide in the Cardiac Arrhythmia Suppression Trial (CAST) trial.

There is a case for a placebo only control arm (not as add on) in an NMO controlled trial. Placebo control can provide unequivocal evidence of proof of efficacy. The number of subjects participating in a placebo controlled study will be smaller than for an active comparator trial. The number of events needed to prove efficacy will also be smaller for a placebo controlled trial. All trials require medically relevant events in order to determine differences between treatment groups. Not all placebo controlled trials are unpalatable. The details of the study design are all important for assessing individual participant risk. Unequal treatment allocation can make this more appealing to patients. Time to first event instead of ARR means that patients' treatment can be amended after the relapse. Providing rescue therapy for treatment of relapse is crucial. The duration of placebo exposure can be limited. Availability of open-label active treatment extension study until approval may make participation attractive for some patients. Use of placebo reduces potential treatment related harm due to unexpected off-target effects until we have a better sense of safety of empirical therapy.

When may the control be a placebo? Freedman B. IRB. 1990;12:1-6 states that placebo could be possible when there is no standard therapy. In NMO, multiple empiric therapies suggest that there is no standard therapy. Placebo could be possible also when standard therapy is no better than placebo - there is scientific equipoise for all current empiric therapies in NMO. Placebo could be possible also when there is doubt regarding the net therapeutic advantage of standard therapy, e.g. some current empirical therapies carry real risks, e.g. malignancy and azathioprine. Also, when standard treatment is unavailable (cost, supply for example rituximab, and MMF may not be generally available). In summary, we need proof to better inform and treat patients, proof stemming from placebo controlled trials.

2.9. Detailed methods to manage risk in a placebo trial

S VanMeter, S Kavanagh, GSK, presented on methods to manage risk in a placebo trial

Risk is inherent in clinical trials. Events are needed in clinical trials to provide needed evidence. It is acknowledged that in the case of NMO, these events are potentially devastating. There are strategies to reduce the risk of devastating relapses. The choice of comparator can influence the number of events needed to show an effect based on the size of treatment effect. However, a smaller treatment difference when comparing to active treatment means a larger sample size is needed than with a placebo controlled trials. For example, a sample size calculation for a clinical trial with Azathioprine as comparator suggests that 76 patient relapses would be observed in a clinical trial. For a placebo comparator, only 30 relapses would be observed in the trial.

Another way to minimise risk is the choice of primary endpoint. In multiple sclerosis, the traditional endpoint is the ARR. Patients are maintained in the trial and monitored for the number of relapses on treatment. This is not possible in NMO with no recovery following relapse. Using time to relapse as an endpoint minimises harm to NMO patients as, upon relapse, patients are put on alternative therapy.

Unequal randomisation can mitigate risk. With an equal randomisation ratio of 1:1, patients have a 50/50 chance of experimental treatment or placebo. With unequal randomisation ratios, there is a smaller chance of being randomised to placebo, potentially increasing patient interest. It also enables the collection of additional safety information, with greater exposure on the test treatment.

With interim analyses, it is possible to look at data part way through study, if this is prespecified and stopping rules for the study have been clarified. It can be a possible way to get to an answer earlier and stop the study, if the experimental treatment is far better or worse than anticipated. No patient is served by being exposed to an ineffective treatment.

Adaptive design options allow modification of study elements part way through the study e.g. if the event rate is higher than expected, then it is possible to adapt the sample size to enroll fewer patients. Another adaptive possibility pertains to the range of different doses. If needed, it is possible to drop less effective doses. Pitfalls exist with this adaptive study design also, as there may be an impact on data collected after the adaptation. Overall, there is a need for a clear answer and, therefore, balance is needed in adaptive study elements and clarity of the result.

An independent data monitoring committee (IDMC) will look independently at data masked in groups. The IDMC will see safety and benefit data and make a masked assessment of risk balance for example, they will stop the trial if it appears unethical to continue due to safety concern or overwhelming efficacy.

Overall, it is considered possible to minimise risk in NMO placebo controlled study and thereby to establish proven efficacy of a new treatment in NMO.

2.10. Patients' views

Irene Wilson - group leader UK Mastocytosis Charity, presented a patient view on the feasibility of placebo only controlled trials in NMO.

This workshop is about controlled drug trials. From my own point of view, I would be very worried starting on a trial just in case out of the blue a relapse occurred especially as so far no relapse has occurred. It must be extremely difficult for drug companies, as trialling new medications is the only way to know if there is a good outcome. From my own perspective, I would be reluctant to take this chance. Maybe however, if a person has experienced relapses they would be more keen to join a drug trial hoping it would help. NMO is life changing. There is no doubt about that and everyday is a struggle and I so hope meds can be found that can help make a big difference to a patient diagnosed with this. Please see Irene Wilson's [full statements](#).

Written patient submission 1 courtesy of Dr Leite

Would I take part in a clinical trial involving a placebo (only) control? The simple answer is no. The risks are too high. The risks for me are 1) physical- a relapse resulting in worsening of existing disability, a new disability (optic neuritis leading to visual impairment) or worsening of symptoms. 2) emotional with the uncertainty, anxiety and worry of being on the placebo and the potential impact of this (i.e. a relapse), the emotional impact on my family and friends. The emotional impact of NMO cannot be underestimated. Being in a 'stable condition' for me has involved being on the right medical treatment and in the right emotional state. In sharing experiences with other NMO patients (across the

world) it seems the success of treatments varies for each individual. This adds to the list of questions I often wonder about...Why does a treatment work effectively for one but not another? A treatment may work now...but for how long? Does it stop working or did it not really work in the first place? Will it work for me? What are the side effects? These vary for individuals too. What if I have tried them all and none of them work? Fortunately for me, that has not happened. Yet...This demonstrates how the uncertainty associated with comparing and trying out existing treatments is bad enough for a patient – without throwing a placebo into the mix.

My first treatment, azathioprine, did not prevent a relapse and I am now trying something different, mycophenolate, combined with prednisolone. There is no guarantee this will work long term; I have, though, been relapse free for longer than my first treatment. The very fact I say I am trying something different implies it is a test; a trial and error scenario where the stakes are high. Being able to cope with the emotional side of NMO, in particular the uncertainty and unpredictable nature of the condition, has been challenging; knowing your treatment only works 'if you don't have a relapse' means I feel, in effect, I am taking part in a 'live' clinical trial with the comparator being my previous treatment.

So would I take part in a clinical trial where an active comparator is used rather than a placebo? The simple answer is no. Considering the risks of coming off the treatment, which is currently working and the side effects, which are known to me and the benefit of starting a new treatment where the efficacy and side effects for me are unknown, there is no question. At this point in time, the risk would not outweigh the benefit. However, if at some stage in the future, I had tried all known treatments and there were no other options, the benefit of trying any treatment versus the risk of no treatment would make me more likely to take part. If clinical trials rely on those taking part doing so because it's their only option, their 'last port of call', for me it emphasises the importance of those trials. This raises a 'moral dilemma' and feelings of guilt at my immediate response of saying 'no' to the questions. I guess the answers are not so simple after all.

Written patient submission 2 courtesy of dr Leite

My background is as a research scientist and lecturer. In any experiment or test of medication I would be very keen to make sure that the trial was properly controlled – usually against a double-blind placebo protocol. But given my history, I *know* that removal of immuno-suppression would be almost certain to lead to increase in relapse rate and probably frequent and severe relapse. Therefore, I would not be willing to take part in a trial if I was at risk of being given a placebo. Given my experience, I believe that the patient themselves can act as the best control. Patients like me, who have tried medication over a number of years, know how they react to different medications. In this case, you are effectively testing different medication in the *same* environment, which is the ideal test case.

If there were good theory for a new medication, I might be willing to try it, and I would know within a few months whether it was effective or not, based on my own relapse rate compared to current rate. I would not be willing to take part in a placebo trial.

2.11. Discussion 2

A variety of opinions were expressed:

- Industry- determination of sample sizes was based on literature and uncertainty is acknowledged.
- Any trial design with ARR could provide an advantage as otherwise each patients can provide little information in the clinical trial. Alternatively, if repeated relapses were to be allowed and the comparator is placebo, after one event, the patients would start to withdraw from the trial, making the study unusable.
- Possibility of a three-armed trial? One company had considered it but this was very challenging and was not very attractive from a patient's perspective.
- For a clean answer for relapse prevention, a placebo design is the best way but there are several ethical ways to go around it. It depends on individual patients/physicians.
- Patient representative, Irene Wilson, isn't keen on participating in a placebo only controlled trial, which would be the response to any patient under a "working" treatment.
- In Berlin, there hasn't been a formal survey but majority of patients are reluctant to come off stable treatment, however, minority of patients unsatisfied with their treatment such as ongoing relapses or side effects (10-20%) would be willing to undergo a placebo only controlled trial.

- Scandinavian patient representative said that the patients represented would not be willing to participate in a placebo controlled trial.
- It was stated that a non-official survey done amongst the patients from the Guthy-Jackson Foundation (US), showed that some patients would undergo a placebo only controlled trial, and were aware of the implications. (see also Discussion 3)

2.12. The ethical consideration of placebo study design in NMO

S Woods, policy, ethics and life sciences research centre (PEALS) Newcastle University, UK, presented on the key issues in the debate from an ethicist's perspective.

In summary, the approach to the use of placebo ought to be precautionary. Risk of harm is compatible with ethical research. Ethical research requires good science. Clinical equipoise allows clinical discretion not to include a patient in a study and this is also compatible with good science and good trial design.

Firstly, the declaration of Helsinki allows that use of placebo controls is ethically permissible but under certain circumstances: ***"Use of placebo. 33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or: Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option".***

It must be recognised that ethical care and treatment needs to be premised upon the best science. It must also be recognised that that research creates vulnerabilities for research subjects which ought to be acknowledged, and that researchers have a duty of care to do no wrong. At least 'Do least possible harm but do no wrong'! There is an important distinction in that *primum non nocere*, first do no harm is well recognised by clinicians, however, medicines often do harm e.g. side effect of medicines, but we think these are justified as we are not aiming at the harms but aiming at the good that might be achieved by using these therapies. In contrast, if patients' vulnerabilities were not acknowledged, or if patients were misled, then this would be a moral wrong. It is not wrong to cause or risk harms when certain strict conditions are met. A risk of some harm may be permissible when the harms are minimised and the harms risked are proportionate (risk/ benefit ratio). Although some time the harms risked are substantial but these are proportionate to the benefits anticipated. A risk of some harm may also be permissible when the harms, if realised, are likely to leave the participant no worse off, the potential extent/ severity of harms may be uncertain/unknown.

Secondly, there are strong moral reasons for conducting scientifically robust research into new therapies. There are equally strong reasons to protect the rights, interests and wellbeing of patients – such reasons are the basis of moral duties. Sometimes these moral duties are in conflict.

For research to be ethical, we must be convinced that it is morally justified to ask appropriate participants (be they healthy volunteers or patients) to run the risk of suffering the known and unknown harms by participating in research. However, this does not amount to an obligation to participate only a reasonable expectation that some will say yes. For those planning and designing (and sanctioning) clinical research broadly, researchers must be convinced that the research design satisfies 1) with an eye to the interests of no particular patient but all relevant patients, and 2) the wider interests of society in bringing effective treatments to patients.

For those primarily concerned with the responsibility for the management of everyday care of patients, as clinicians, then they must be persuaded that such interests are not in conflict or they must be permitted the appropriate discretion to form a different judgement e.g. that it would not be in the interests of this particular patient to enter a placebo controlled trial – this seems consistent with clinical equipoise (Freedman B. NEJM; 317:141-5, 1987, Miller PB, Weijer C. Kennedy Institute of Ethics Journal 13:93-118, 2003). Discretion is allowed so that particular judgements can be made based on empirical information in individual cases.

Every doctor has a duty of care to his or her patients because every person has a duty not to wrong others. Doctors are trusted to make good judgements as to what will help (not wrong) their patients.

Patients must have the best advice available to them and, alongside the guidance of a trusted physician, they must also have access to the reasoning of those who have planned (an ethically approved) research project. They must be allowed the freedom to make their own decision without constraint which is the basis of informed consent and autonomy.

In order to determine what is the reasonable and morally prudent position for NMO patients, then a number of questions need to be addressed regarding the existing treatments and the proposed clinical trial.

1. Is there a standard of care? How has the standard been established – against placebo or no treatment? Are there common examples of 'on treatment' relapses? Are there common examples of 'off treatment' remissions? Having a detailed answer to these questions helps us understand the reasonableness of a placebo controlled trial.
2. Research design; is a placebo necessary? We have heard arguments for and against placebo only controls. Is it necessary to withdraw or withhold standard treatment? Will there be the smallest possible placebo group? Will the study involve a cross-over or an open label extension? Will 'on placebo' relapses result in immediate withdrawal and administration of rescue therapy. We have had these highlighted as potential options.

Finally, we must avoid an elitist approach and recognise the patient voice. Patient involvement is vital as patients have a reasonable expectation that research will happen (right to research). They also have a reasonable expectation that they will make a contribution to the research effort (duty to consider participation) and a reasonable expectation that they will have a voice at the research table (includes upstream consultation with patient organisation throughout the whole process of research). Indeed, a member of a patient forum said recently 'Why wouldn't we be at the table?'

Placebo use ought to be precautionary and ethically justified, meaning that clinical equipoise should be in place. The risk of harm is minimised with the least possible exposure to placebo. It is essential that there is an appropriate form of ethical review and consultation with patient groups.

2.13. United States perspective- regulatory

W Chambers, FDA, US, presented his personal views on the requirements to support the risk benefit assessment for relapse prevention in NMOSD

For new drug application (NDA) or biologic license application (BLA), evidence from adequate and well-controlled investigations are needed to determine whether there is substantial evidence to support any claims of clinical effectiveness. The elements of adequate and well controlled trials include the following seven items:

A clear statement of the objectives, a design that permits a valid comparison with a control to provide a quantitative assessment, an assurance that patients have the condition, assignment between groups that minimises bias, minimisation of bias amongst subjects, observers and analysts, a well defined and reliable method of assessment, analysis of the results.

Specifically with regard to trials for the US, the FDA would be looking for superiority compared to control which could be any of the following: superiority to current standard of care, superiority as an "add on" to another therapy, superiority to no treatment. There would be an expectation of randomisation between arms to minimise bias.

Depending on the claim, NMO may be reviewed in the FDA ophthalmic group or the neurology group. From an ophthalmic perspective, a measure of visual function would be expected such as measurement of visual function including but not restricted to visual acuity. Possible claims could be based on improvement of, or prevention of loss of visual function. Clinical relevance is equivalent to doubling/halving of visual angle as applicable to high contrast or low contrast visual acuity or other measures of visual function. Nerve fibre layer as anatomic measure is not currently acceptable as an endpoint in that, to date, this not match clinical function. The number of relapses of optic neuritis as an endpoint is of questionable value, as it is the level of final visual acuity that makes the difference. Regarding duration, the expectation is that patients would be following for at least one year but this does not mean you cannot have time to event and switching of therapies; a one year or greater timepoint is recommended due to known potential for optic neuritis to improve with time. Efforts must be made to minimise bias, with masking of patients, investigators and analysts. Ancillary treatments and timing of study visits should be the same for all groups. The analyses must evaluate the likelihood

that any findings are due to chance with two sided confidence interval $p < 0.05$, given the potential for harm as well as benefit with an experimental treatment. Adjustments for multiplicity and for interim looks at the data must be made. With an interim analysis, where the trial is not stopped, there may be a cost in needing additional recruitment of patients.

2.14. EMA view

MM Rosa, Faculdade de Medicina de Lisboa, SAWP, Infarmed, PT considered the working EMA position on possible comparators.

Why is there unease in the EU with placebo in NMO? Clinicians have deontological ethics (holds that the basic standards for an action's being morally right are independent of the good or evil generated) deep rooted with virtue imposed by society even more. Clinicians have a strong duty to protect patients. We have heard this morning from an alternative perspective of Teleology (theory of morality that derives duty or moral obligation from what is good or desirable as an end to be achieved) which favours use of placebo because the final outcome of development will be cleaner, and quicker.

The working EMA view was based on the following aspects in NMO: the benefits with best medical care, the risk of best standard of care, the risk of withholding / tapering treatment and the risk of uncertainty in knowledge of benefit / risk balance when establishing comparison to best care, and availability of the comparator in the Member States for external validity. The risk of uncertainty in the knowledge of benefit / risk balance depends amongst other factors on study population selected (NMO / NMOSD, AQP4-IgG positive / negative, previously immunosuppression / ongoing / naïve, post immunosuppressant failure).

It is important to take into account the views of patients with regard to the acceptability of placebo as add-on or not, as well as those of clinicians, investigators and sponsors.

Please see Section 1 for the updated EU regulatory position.

2.15. EU clinical view

MI Leite, NMO and autoimmune encephalitis services, University of Oxford, UK, presented an EU clinical view on placebo controlled trials in NMOSD to support the risk benefit assessment for relapse prevention.

There is a broad consensus amongst EU clinicians with expertise in managing NMO on current treatments for NMO. Even prior to the discovery of AQP4-IgG, it was clear to those treating NMOSD patients that immunosuppressants were beneficial in the prevention of further attacks. Subsequent (mainly retrospective) studies showed clearly that immunosuppressant medications prevent attacks in this potentially devastating disease mediated by AQP4-IgG. It is understood that there are limitations in that these are non-randomised studies but knowledge is also gained from clinical experience. There are small open label studies (e.g. rituximab and eculizumab) and an unpublished retrospective analysis showed that immunosuppressant medications not only prevent attacks, but may also reduce their severity. Attacks can be devastating, with a high risk of morbidity and mortality. It is vital that we aim for no relapses using the best available treatments. There is a vast consensus on early and continuous preventive treatment. It is standard of care in great majority of centres worldwide that patients with a first episode of AQP4-Ab mediated disease are offered chronic immunotherapy due to their high risk of relapse. However, if the current immunosuppressive treatments fail, and we know that some patients do not respond or lose response, we need more and better medications for NMO. Unfortunately, a placebo-controlled trial, will not answer the question of superiority of efficacy of an experimental treatment compared to currently used therapy. It is virtually guaranteed that any immunosuppression will be more effective than doing nothing at all. We need to know whether or not these new drugs will be superior and safer than current immunotherapies, that we already know help control disease activity in NMOSD patients, and whether or not the drugs under investigation are valuable in patients that fail to respond to other treatments.

An EU survey was conducted amongst neurologists treating NMO. There were 19 responses out of 30 possible, covering 9 countries (Austria, Denmark, France, Germany, Poland, Portugal, Spain, Turkey, UK). Of these, 11 clinicians manage only adults, 3 only children, and 5 both adults and children. All 19 responded to all questions. See below:

Questions and responses in EU survey of neurologists

	YES	NO	May be	Some- times
Q1 Do you treat all the AQP4 positive patients chronically from the time of diagnosis with any form of standard immunosuppression?	18			1
Q2 Do you feel that there is enough clinical evidence for the use of the standard immunosuppressive medication in NMOSD?	15	3	1	
Q3 Based in your experience and /or knowledge, do you agree that a proportion (~15-20%) of patients respond poorly to the standard preventive treatments?	19			
Q4 When patients fail to respond to standard immunosuppressive prophylactic treatment (breakthrough), do you usually change medication or doses to prevent more effectively further attacks?	18		1	
Q5 And would you agree with the clinical view that those patients (mentioned in question 4) need to be considered to change to a different treatment; i.e. would be candidates to a new immune medication?	19			
Q6 Would you sign up to a clinical trial where patients with active disease/fail to respond to standard care are randomised to be in a placebo-control trial comparing active agent vs no treatment?	3*	16		
Q7 Do you agree that we should now be looking for immune treatments that are superior to the standard ones, and, therefore, clinical trials that compare new agents with standard ones?	19**			

*Yes, under a well defined ethical statement** (placebo RCT add on would be the trial design to consider)

The great majority of EU neurologists responding to the survey would not sign up to enroll patients in a drug trial for NMOSD with a placebo only arm. All respondents agree that the key question is about the potential superiority of new agents over the current standard of care. Currently, there are no established markers to predict time to next relapse, relapse severity or relapse outcome. These uncertainties contribute to increase the clinical vulnerability of patients in a placebo only arm. As it has been happening in other autoimmune or inflammatory diseases (e.g. SLE, GCA) with the same immunopathogenic mechanism and in transplantation, it should be possible to transfer evidence from similar diseases. Adequate information for patients before participating in any trial is crucial; patient must be informed that the next relapse can leave them blind, wheel-chair bound, or may cause death. The term “rescue therapy” in the informed consent or elsewhere is a misnomer in that often there is no or only incomplete recovery from NMO attacks.

2.16. Discussion 3

Overall range of discussion:

- Regarding the non-official survey done amongst the patients from the Guthy-Jackson Foundation (US): there were comments questioning the survey methodology. Patients were not asked directly if they would find a placebo only controlled trial acceptable.
- Industry feels that there is no standard of care, the immunosuppressive therapy is an unproven therapy and fits only the American Academy of Neurology “U” class, which should be disclosed to the patient when starting on immunosuppressants.

- Clinician- full disclosure is made to patients regarding risks, uncertainties and knowledge of level of efficacy.
- EMA acknowledged the low level of evidence but recognised that it is still some evidence, and not conflicting either which is also important. It would be quicker and cleaner to have data from RCTs, but in order to have new medication, it is necessary to assess the evidence available and all aspects of the proposed designs.
- Clinician stated that FDA had influenced the study design of companies that initially were standard of care controlled studies. MedImmune responded that they were wholly convinced of the appropriateness of doing a placebo-controlled trial.
- W Chambers (personal view) remarked that placebo-controlled trials are not mandatory for FDA and that superiority trials to another comparator should be perfectly acceptable.
- Clinician pointed out to industry that standard of care is largely decided by professionals and patients using those medicines and the current level of knowledge.
- FDA definition of relapse matters; if defined a relapse with clinical consequences e.g. 3 line of Visual acuity loss, this could be acceptable.

2.17. Endpoints - clinical view

A Jacob, The Walton centre – Liverpool, UK, presented a clinical view on possible endpoints in trials for relapse prevention in NMOSD.

The two most important, measurable, biological aspects for a patient with NMO that we are trying to reduce or modify with a drug are relapse and disability. Can we replace these with surrogate endpoints? Can we use parameters from MS? i.e. 1) relapse related- time to first/second relapse, annualised relapse rates (ARR), relapse duration severity by neurologic rating scale, relapse free proportion 2) disability related- sustained EDSS change months-years, ambulation index, arm function, multiple sclerosis functional composite (MSFC), and 3) surrogate- MRI related changes.

Can we use parameters from spinal cord injury (SCI), although traumatic SCI typically has no relapses? Such endpoints include disability measures- the American spinal injuries association scale (ASIA) disability scale (A-E). Note a 2 point improvement in ASIA is the primary endpoint in UK study (STRIVE) in acute transverse myelitis. This is well validated but cannot measure non spinal cord dysfunction. Surrogate electrophysiological endpoints in SCI (SSEP) are not correlated to clinical improvement.

Relapse vs disability - which should be the primary endpoint? The aim is to prevent disability (of various types) but disability in NMO is a direct consequence of the relapse. Spontaneous gradual progression of disability like in MS is very rare in NMO. Thus NMO relapses are a clinically relevant measure.

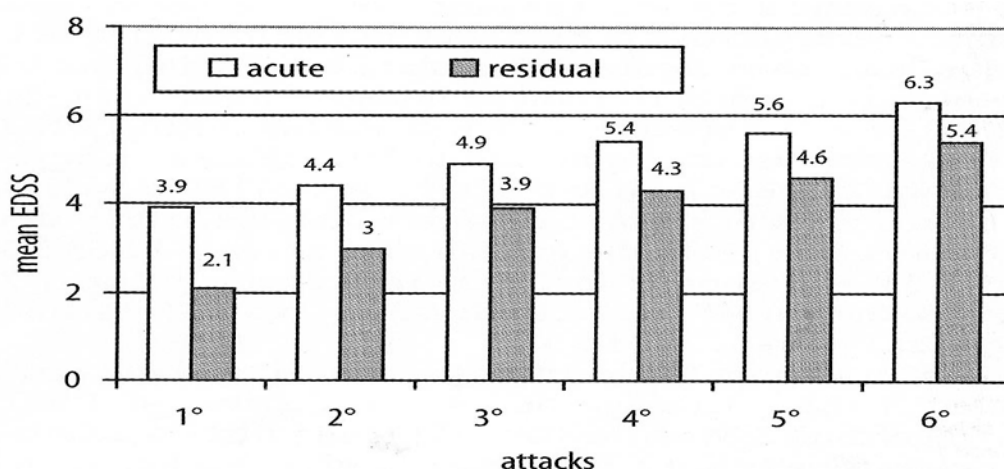


Fig. 2 Mean EDSS score during and after the acute phase of the first six attacks

Ghezzi A et al. J Neurol 2004; 251; 47-52

The characteristics of a relapse that needs consideration are: definition of relapse, whether a strict protocol definition or investigator discretion is allowed, time to first relapse or annualised relapse rates severity of relapse, and types of relapse (myelitis, optic neuritis, brainstem events).

A definition of relapse based on clinical practice is a new onset neurologic deficit or worsening of existing one with an objective change (for at least 24 hours), related to NMO on a background of stability of >1 month. It is practicable in clinical trials to allow for clinician's judgment (investigator defined) in identifying relapses but this may introduce bias based on experience, knowledge and other subjective elements. Therefore, do we count only protocol defined relapses for the primary endpoint? This can add further objectivity. For example, with specific change in EDSS e.g. 1 point, or on the functional system score (FSS) of EDSS e.g. 2 points. This should suffice for vast majority of relapses but occasionally this may not capture a true relapse, for example severe neuropathic pain and itch with MRI findings, or intractable vomiting and MRI abnormality. Is the solution to think of a variety of such scenarios and make objective definitions with the addition of MRI criteria? Which is the appropriate endpoint in NMO: time to first relapse or annualised relapse rates? There are pros and cons of each measure; See below.

Time to first relapse (TFR)	Annualised relapse rates (ARR)
Pros:	Pros:
Patients can exit study if treatment ineffective	Standard familiar measure
Reduces disability accumulation	
Recruitment better	Long term effects identifiable
Shorter studies	
Cons :	Cons
Long term effects not demonstrable	Unless all patients stay in for a minimum period (denominator), skewed ARR
Slow acting drugs may not have chance to become effective; need time to second relapse or such	
Each patient contributes only one event	

It appears that TFR is the most appropriate measure to limit exposure to a potentially ineffective drug in a disabling disease. Attack severity can vary owing to many patient, physician and treatment factors. Should all attacks be considered the same? Scales that can be used to assess severity include the EDSS functional scale, Optic Spinal Impairment Scale, and ASIA. Can we develop an attack severity score as a product of relapses and severity? No such a score exists currently. This may allow distinguishing a clinically meaningful difference if scores used, when otherwise there may be no apparent difference if relapses are merely counted.

Amongst secondary end points, disability is very important. The main categories are spinal cord/ brainstem related, motor (weakness, spasticity), sensory (numbness and pain), bladder, bowel, sexual function, and vision. How do we measure these? We can use multi-system scales. Is EDSS suitable? This is familiar and well validated in MS research, but cerebellar and cerebral FS are not really applicable in NMO, as cognitive and cerebellar dysfunction is limited in NMO. The other FSS are valuable (brainstem, pyramidal, sensory, bladder bowel, visual). Multiple sclerosis functional composite (MSFC) has potential problems in NMO. The cognitive element adds little value and spinal cord function is poorly assessed, although may be of some use. The Optic Spinal Impairment Scale is derived and modified from EDSS. There are no formal psychometrics supporting the scale and it is not widely used, however, it may be worth validating this scale and using it more frequently. System specific scales; spinal cord specific scales include ASIA scale and Spinal cord injury, bladder bowel data sets. For vision specific scales, there are numerous scales but none are specific for optic neuritis.

Table I. Summary of vision-specific instruments

Questionnaire	No. of items	Eye condition	Subscales	Item pool development	Psychometrics	Mode of administration
Activities of Daily Vision Scale (ADVS) ^[9,10,14]	20	Cataract, age-related macular degeneration	Night driving, day driving, distance vision, near vision, glare vision, overall score	CB	IC, TRR, CV, DV, R	Interviewer
American Society of Cataract and Refractive Surgery–Cataract Data Collection Form (ASCRS-ACDCF) ^[15]	31	Cataract	Mean functional impairment score	NR	NR	Self
Cataract Symptom Scale (CSS) ^[16]	15	Cataract	Total score	PB	IC, TRR, CV	Interviewer
Catquest ^[17-20]	37	Cataract	Disability/daily activities, cataract symptoms, activity, driving, employment, global health rating, total score	PB, CB, LB	IC, TRR, CV, DV, R	Self
Daily Living Tasks Dependent Upon Vision (DLTV) ^[21,22]	22	Cataract, age-related macular degeneration	Total score	PB, CB	IC, CV, DV	Interviewer
Quality of Life in Patients with Graves' Ophthalmopathy (GO-QOL) ^[23]	16	Graves' ophthalmopathy	Visual functioning, appearance	PB, CB, IB	IC, CV	Self
Houston Vision Assessment Test (HVAT) ^[24]	11	Cataract	Visual disability, non-visual physical disabilities, total score	PB	IC, CV	Interviewer
Impact of Vision Impairment (IVI) ^[25,26]	32	Cataract, glaucoma, age-related macular degeneration, diabetic retinopathy	Work and leisure, household and personal care, mobility, consumer and social interaction, emotional reaction to vision loss, total score	PB, IB	IC, TRR, CV	Self and interviewer
Madurai Intraocular Lens Study (MIOLS) – Health-Related Quality of Life (HR-QOL) Questionnaire ^[27]	12	Cataract	Self-care, mobility, social, mental, total score	PB, CB, IB	IC, TRR, CV, R	Interviewer
Madurai Intraocular Lens Study (MIOLS)-Visual Functioning (VF) Questionnaire ^[27]	13	Cataract	General, visual perception, peripheral vision, sensory adaptation, depth perception, total score	PB, CB, IB	IC, TRR, CV, R	Interviewer
Miedziak's instrument ^[28]	54	Stargardt's macular dystrophy	Total score	PB, IB	NR	Self
Measure of Outcome in Ocular Disease (MOOD) ^[29]	21	Ocular melanoma	Vision, impact, total score	PB	IC, TRR, CV	Self

There are aspects of disability that are not measured conventionally, such as severe intractable pain which should be incorporated into clinical trials. Pain is a significant issue in NMO.

Surrogate markers are not available, as AQP4-IgG titres do not correlate with disease severity or relapse in a predictable universal manner across patients. Also, MRI is not validated as a surrogate endpoints and there are often no clinical correlates.

Quality of life (QoL) is very important in NMO. We know QoL is poorer in NMO but there are no specific NMO-specific QoL measures. The approach is to use standard measures (SF36, EQ5D), spinal cord specific measures (spinal cord injuries quality of life), and those related to vision (low vision quality of life)]. Patient reported outcome measures (PROM) are an important aspect but no specific measures have yet been developed in NMO.

In summary, from a clinical perspective, a primary outcome should be time to first relapse. For disability, there is no good scale but presently EDSS and its FSS can be used, also using elements from SCI (ASIA, SCI of bladder bowel function, OSIS). Pain scales need to be considered. Specific QoL scales and PROMS need to be developed together with paediatric versions of relevant scales. Health economics aspects are a necessary requirement and care-giver burden should be assessed.

2.18. Endpoints – industry

A Perera, Chugai, presented an industry view on short and long term endpoints.

The challenge is that the primary endpoint must provide data to meet the evidentiary standard for approval, providing evidence of substantial evidence of effectiveness/clinical benefit in the target patient population. There are no EU regulatory guidances in NMO. However, some help can be derived from existing guidances. The CHMP guideline on clinical trials in small populations (CHMP/EWP83561/2005) is relevant wherein EMA acknowledges the challenges of small populations and (in our interpretation) adopts a pragmatic view in the guidance of what is acceptable in terms of choice of primary endpoint. The primary endpoint according to the EMA guidance - must be clinically relevant, measurable and interpretable. Examples are provided of 'grades' of acceptable endpoints:

'Hard' endpoints (cure of disease, overall survival), or 'intermediate' such as time to disease progression, and relief of symptoms may be an acceptable endpoint.

From a disease specific perspective, there is no guideline for NMO but guidelines exist for the related and more common demyelinating disease of multiple sclerosis which could be considered a reference point. Other disease guidelines may be helpful to NMO such as the *EMA guideline on clinical evaluation for stroke and systemic embolic events (SEEs) in patients with non-valvular atrial fibrillation* (EMA/CHMP/450916/2012) which proposes a composite primary endpoint of time to first stroke and number of SEEs. Stroke could be viewed as more similar to NMO than MS because of permanent damage at each event. Candidate primary endpoint(s) for NMO include progression in disability as assessed by annualised relapse rate (ARR), or progression in disability as assessed by time to first relapse (TFR). Regarding surrogate endpoints, candidates have been proposed but none are validated for NMO (serum anti-aquaporin-4 antibody levels, MRI).

The comparison of TFR vs. ARR is made from three perspectives: ethics and patient/clinician acceptance of study, the duration of double-blind period, and study statistics.

From the perspective of ethics and patient/clinician acceptance of study:

TFR	ARR
PROS: Avoids ethical issue of keeping patients on same trial treatment after 1st relapse. Each relapse in NMO has permanent and major consequences in terms of disability. Once relapse occurs, alternative treatment should be given (effective, unlicensed alternatives are available) - TFR endpoint allows this. Makes trial participation more attractive to patients and clinicians. CONS: ---	PROS: --- CONS: Clinical experts have advised that ARR not an acceptable endpoint for placebo-controlled NMO trials because neurological effects of relapse are permanent, thus patients need to be offered alternative treatment at 1st relapse on trial. Even if ARR were 1^o endpoint, relapsers are likely to be withdrawn from trial for alternative treatment, therefore duration of placebo-controlled efficacy and safety data would be capped. No approved active controls are available in this indication.

TFR vs. ARR: duration of double-blind study period

+	ARR
PROS: For industry – potential for a trial of shorter duration (dependent on relapse rate for the study population). CONS: Possibility to leave DBT for OLE at 1st relapse (for ethical reasons) means that placebo-controlled safety/immunogenicity database will be limited and variable in duration. At end of trial, placebo patients will have different durations on study treatment (since relapsers can switch to study drug in OLE), thus interpretation of data is complicated by informative censoring. Evaluation of 2^o endpoints is complicated by different durations of treatment and switch from placebo to active. Unable to demonstrate long-term efficacy after 1st relapse.	PROS: In theory, endpoint would allow collection of efficacy data (prevention of relapse = maintenance treatment) over a longer and fixed period of time – but probably not in practice. If patients required to stay on DBT for at least one year, better duration of placebo-controlled safety data might be available for comparison with study drug. CONS: ---

TFR vs. ARR: study statistics (1)

TFR	ARR
PROS: Availability of powerful statistical techniques for survival analysis. Kaplan Meier survival curves and the Cox model for multivariate analysis make the interpretation of results straightforward. Censored data easily managed e.g. patients given rescue treatment by site without meeting protocol-defined criteria for relapse, according to independent reviewers.	PROS: Experience has been gained with this 1^o endpoint as in MS trial. More data are available for ARR than TFR in NMO from publications but none describe controlled trials.

TFR	ARR
CONS: Sample size calculations are based on assumptions since few published data available on TFR in NMO. Shape of distribution of post-baseline ARR has been assumed on the basis of MS trials because few NMO data are available. Information on relationship between TFR and ARR in NMO is not available and TFR has been estimated from ARR, assuming shape of distribution of relapse-free rate. Sample size calculations assumes constant hazard rate for TFR but clinical information is that relapses may cluster, occur after treatment change, or occur seasonally.	CONS: Method does not give information on timing of relapse events. Methods of analysis of ARR do not easily allow for censored data. When follow up period is around one year and number of events per year is low, statistical power of ARR is lower than TFR e.g. if ARR 0.3, probability of a patient having 2 or more events in one year is 5% (Sormani et al 2013). Less sensitive analysis method is likely to require larger numbers of patients in a small patient population.

In summary, statistically there are pros and cons for both approaches. Practically and ethically, TFR is a more attractive approach because patients can move to alternative treatment on relapse. Event-driven analysis is recommended in EMA draft guidance for a condition which similarly affects the CNS irreversibly (e.g. stroke).

Acute and recurrent episodes of optic neuritis and transverse myelitis (“relapses”) is the defining characteristic of NMO as it leads to severe, permanent, relapse-related neurologic impairment such as blindness and paraplegia. Considerations in the context of a clinical trial are that evaluation of a relapse must be objective and measurable; however, what tool should be used to define a relapse in NMO and who should define the relapse?

Kurtzke expanded disability status score (EDSS) is considered the gold standard for measuring the occurrence and severity of a neurological relapse. It is accepted by regulatory agencies as the appropriate tool evaluating changes in disability resulting relapses in MS studies. EDSS appears the most appropriate tool for assessment of occurrence of relapse and, hence, disability in NMO also. There are a number of areas for discussion; when should the EDSS be performed in relation to onset of symptoms and timing of acute therapy for relapse. i.e. as soon as symptoms onset, or before treatment or is residual disability more important. What change is EDSS is considered a reliable, permanent and clinically meaningful change in disability? Who should perform the EDSS: study physician (is this biased?) or independent adjudicator? Should other tools for measuring changes in disability in NMO other than EDSS be used? Should a co-primary endpoint be considered in NMO? There is a lack of consensus on a single most important variable.

Secondary endpoints are very important. These can support the primary endpoint – giving a more “holistic” characterisation of therapy benefit. These are important also for health technology assessment and can be a point of differentiation from competitors. These can include severity of relapse, QoL, caregiver burden, other disability scores.

Post approval commitments are to be expected. For an approval based on small population clinical trials (and exclusion of subpopulations), ongoing risk/benefit monitoring (to detect previously unrecognised positive or negative effects associated with a drug) has a greater imperative. What are the appropriate methods for ongoing monitoring of efficacy and safety and the pros/cons of each in NMO? Further trials and meta analyses appear unlikely, unless conditional approval is given or significant risks in the registration trial are identified. Therefore, possibly epidemiological studies, data collection using patient registries for post-marketing research or other types of active surveillance may be required.

2.19. Discussion 4

A range of views were expressed:

- Academic respects FDA position, for e.g. in Optic Neuritis on number of relapses but do not completely agree, because with every single relapse there is an accumulative deficit in this condition. With regard to outcome, OCT as it takes very little time, it's very accurate and it's ideally posed to assess quantitative cumulative deficit.
- FDA answers that OCT unfortunately doesn't match visual acuity, and the company assumes all relapses are the same, but the problem is that it's not the case.
- EMA answers that relapses are defined on a clinical event. OCT could be valued as an additional endpoint, but as a trigger for relapses, it is problematic.

- Capturing ON in sensitive manner; an operational definition based on multiple clinical measures needs to be elaborated for example to capture new events in already severely affected patients acuity, afferent pupillary defects, or pain to manage such patients. None of the available scales for vision adequately capture the complex aspects of vision involved.
- In a design with a time to relapse rather than an annualised relapse rate, patients will be followed for different periods of time and it will be impossible to know the importance and severity of the relapse, without something to quantify the amount of disability.
- Expert suggested stratifying based on severity of relapses, e.g. multiply each relapse by a severity measure.
- EMA noted that for very rare diseases, focus on what is feasible. A relapse should be a clinically defined event, in terms of a change in the patient, measurable objectively. Disability as an endpoint at end of a study is also very important for EMA. The absence of an agreed consensus on relapse is a challenge.

2.20. Development of drugs in paediatric NMOSD - clinical view

C Hemingway, Great Ormond Street Hospital, UK, presented the clinical view regarding development of new medicines in paediatric NMOSD.

Until recently, there was a paucity of population data on paediatric demyelinating disease, but recent studies on all inflammatory demyelinating conditions have given incidences ranging from 0.66/100 000/y Holland to UK 1.1/100 000/y. A surveillance study was carried out in the UK 2009-2010 on first onset CNS inflammatory demyelination in patients less than 16 years of age. Of 4095 clinicians (ophthalmologists, paediatric neurologists, paediatricians) surveyed, 90% provided returns with 222+ notifications. From this surveillance study, of the 125 children who satisfied the inclusion and exclusion criteria for first CNS demyelinating event, 2 presented with NMO (1 under and 1 over 10 years) which in the UK population would be about to 1-2 new cases per year, or an incidence of NMO of 1 in 5 million. Subsequently, a retrospective case ascertainment and note review of UK paediatric (<17 years) NMO cases was conducted based on Wingerchuk 2006 criteria. Descriptive statistics, univariate associations, and Kaplan-Meier life table analysis were used to explore differences between AQP4 positive/negative cases and predictors for relapse.

Twenty-two cases were ascertained of which 86% were female and 60% were AQP4 +. Age of onset was about 10 years. At onset, 75% had a presentation which included optic neuritis. In other paediatric studies of NMO, optic neuritis was a presenting feature in more than 50% of cases, with attacks often bilateral and /or involving the chiasm. Brain lesions were common. Just over 66% cases had abnormal brain MRI at presentation. Whereas in adults, brain lesions are often silent, in paediatric NMO, these are often symptomatic. Approximately 86% cases were relapsing and in those with AQP4-Ab positivity, there was a higher annualised relapse rate (ARR AQP4 IgG- = 0.38/yr and AQP4IgG+ = 0.70/yr). Comparing AQP4 IgG positive and negative cases, the time to first relapse was significantly shorter in AQP4IgG+ children, with more than 50% experiencing their first relapse within 1 year. Brain lesions occurred more commonly and earlier in paediatric NMO than in adult NMO and were found throughout the brain. These were often large lesions. The differential diagnosis includes osmotic myelinolysis, mitochondrial or metabolic disorders, ADEM, multiple sclerosis, isolated optic neuritis, isolated TM, and tumour of brain/cord. Permanent disability is attack-related in NMO. Visual impairment is common in paediatric NMO and particularly common in AQP4 IgG + patients.

+	AQP4 neg	AQP4 pos
At least one eye 6/60 or worse	0/8	11/14 (79%)
Severe visual impairment (blind)	0/8	7/14 (50%)

Three patients (14%) were also wheelchair dependent on follow up. Similar findings have been published from other study groups on age of onset, seropositivity and outcome.

Regarding treatment, there are no RCTs in paediatric NMO; all practice is based on adult studies. Clinicians use consensus statements as produced by the paediatric MS study group. Acute attacks are treated with 5 days of IV steroids ± IV immunoglobulin. Severe exacerbations are treated with

plasmapheresis. Once a diagnosis of NMO is confirmed, immunosuppressants are offered. A wide variety of disease modifying drugs are used including AZA, Prednisolone, MMF, and Rituximab.

There are some differences between paediatric NMO and adult NMO: paediatric onset NMO is rarer than in adults and there is a monophasic illness in about 20%. The clinical presentation is similar but there are some age dependent anatomical susceptibility differences: Optic neuritis and secondary severe visual impairment are more common in Paediatric NMO; in addition, the brain spectrum affected is wider, MRI lesions are larger, found in areas not AQP4 rich, and are often symptomatic. LETM is less specific in the paediatric setting, also occurring in 10% MS spinal lesions.

Regarding long term outcome, there are very few data; compared to patients with adult onset NMO (n = 101), patients with paediatric NMO (n = 12) had a longer median time to EDSS 4 (20.7 vs 5.3 years; $p < 0.01$) and EDSS 6 (26 vs 8.5 years; $p < 0.01$). However, because onset is in childhood, the age of this event is younger than adult onset NMO. It is an open question whether age is a major determinant of remyelination, accounting for the differences seen between adults and children in NMO.

Regarding possible future trials in children, the difficulty is that the condition is very rare: a trial to reduce an ARR from 0.70 to 0.35 would need 84 patients/arm. Thus, a very long international multicentre study would be needed. On the positive front, diagnostic criteria are available, there is a biomarker and it is known that relapses are an important prognostic marker for disability. Children and young people want trials, and want evidence based medicine to inform their care.

Involving children in trials necessitates a careful assessment of risks, although some risks are not predictable. Questions posed in the trial must be carefully thought through to answer the data needs of clinicians. Risks can be minimised by good trial design and treatment through referral centres by trained personnel, and adherence to well established paediatric research standards. It is important to start with a registry of all paediatric NMO patients. As in the oncology paediatric service where great improvements have been made, all children treated could be recruited into studies. Trials in paediatric NMO should occur alongside adults phase III trials to obtain at least PK and some data before such agents are used off label in children.

2.21. Development of drugs in paediatric NMOSD: industry perspective

J Glover independent pharmaceutical physician presented on development of new medicines in paediatric NMO from an industry perspective.

Paediatric NMOSD is very rare (Tillema and McKeon 2012). Estimates are based on small numbers which may be unreliable. The median age of diagnosis of NMOSD is 10 to 14 years. The youngest has been diagnosed just under the age of 2 years. There are varying proportions of white to non-white patients in case reports from Europe and the Americas. NMO-IgG positivity ranges from 16% to 80%. As in adults, NMO-IgG seropositivity is associated with a relapsing course in paediatric patients. It would appear more justifiable to recruit children in clinical trials for treatment with immunosuppressants who are NMO-IgG positive and with relapsing disease. It seems that NMO/NMOSD appears to be considerably less commonly diagnosed in children than adults.

The starting industry viewpoint on paediatric NMO/NMOSD is that conducting clinical studies will be very difficult. The number of patients recruited per site is likely to be low, which means the cost to Sponsor per child recruited is high and the study duration will be long. Children may require specific formulations/presentations and/or toxicity studies, adding to development costs. There is a potential to delay adult marketing authorisation, despite the regulatory aims, unless paediatric studies are waived or deferred. The paediatric indication is not likely to be profitable in the EU, and there is an increased potential product liability with use in children. It is not an attractive proposition to industry but needs to be addressed.

Regarding the potential paediatric investigation plan (PIP) content in NMO/NMOSD, the PIP content or waiver request must cover all paediatric age groups (pre-term, term newborn, infants/toddlers, children 2 – 11 years, adolescents 12 – 16/18 years). For each age subset, the PIP may propose full, controlled paediatric clinical studies concurrent with adult development, or limited paediatric clinical studies with extrapolation from adults, or deferred paediatric clinical studies or a waiver of paediatric clinical studies. The PIP will depend on the nature of the drug, the amount of adult and paediatric data already available with that drug/class of drug (in terms of PK/PD, efficacy, safety and immunogenicity) in NMO and other indications.

Is there potential for a waiver in NMO/NMOSD? A waiver can apply to condition for the whole paediatric population (full waiver) or to age subsets (partial waiver). There is no class waiver in NMO. A product-specific waiver can be applied for on the following basis: either the medication or class of medications is likely to be ineffective or unsafe in all or part of paediatric population (unlikely to apply), or the disease or condition does not occur in all or part of paediatric population (but does occur in some), or the specific medicinal product represents no benefit over existing treatments for paediatric patients (but there are no approved treatments in NMO).

It would appear that some paediatric clinical studies are likely to be necessary for most drugs in NMO/NMOSD for EU MA purposes, because adult and paediatric disease are not fundamentally different.

Is there potential for deferral in NMO/NMOSD? A company can apply for deferral of initiation and/or completion of some or all of measures in PIP if, for example paediatric studies will take longer, if it is appropriate to conduct studies in adults prior to children for ethical reasons, if adult PK data are required to determine a dosing regimen for paediatric studies (e.g. if drug not approved for other paediatric indications), if additional non-clinical studies necessary prior to paediatric studies or if additional formulation work required prior to paediatric studies much depending on whether the agent has been studied/approved in adults in same indication or in other, extrapolable paediatric indications

What is the potential for controlled clinical studies in NMO/NMOSD? There is a very restricted population available, requiring many sites. Such a study probably would only involve patients with relapsing, NMO-IgG positive NMO, in trial requiring intensive treatment, depending on the drug type, further restricting the population.

A multi-company approach (one control group, multiple active arms) could perhaps be considered but this has significant challenges.

What is the potential for extrapolation from adult data in NMO or from other indications to avoid unnecessary studies where feasibility is restricted. The most common extrapolation is from adults to children or between paediatric subsets. This requires expected similarity between source and target populations in disease (aetiology, pathophysiology, clinical presentation, diagnosis, treatment, prognosis), PK/PD relationship, likely response to study treatment in terms of efficacy, safety and (for biotech) immunogenicity. This requires a plan involving an extrapolation hypothesis, probably using pharmacokinetic/pharmacodynamic (PK/PD) modelling, limited testing of predicted PK/efficacy/safety in target population, testing "fit" of results to hypothesis, development of dosing recommendations for target population, possibly post-marketing commitment to monitor success of prediction.

In NMO/NMOSD, adult and paediatric NMO/NMOSD appear similar (in terms of aetiology, pathophysiology, clinical presentation, diagnosis, treatment, prognosis) with some minor differences. Adult treatments have been used in children with success (according to case reports and physician experience) but without clinical studies. Extrapolability of PK from adult to children is also dependent upon the individual drug (but for most monoclonals PK is affected by body weight). The availability of PD markers may depend upon individual drug mechanism of action as there are no proven, common PD markers for NMO/NMOSD as yet. Extrapolability of efficacy from adults to children may depend upon individual study population factors e.g. proportion of NMO-IgG positive/negative patients, background immune suppression or not etc. EDSS has been used for efficacy assessment in children as in adults. Time to first relapse could be used, adding other validated measures of disability/QoL. The ability to extrapolate safety/immunogenicity may depend upon experience with the same drug/class of drugs in other indications.

In summary, from an industry perspective, the paediatric NMO/NMOSD population is extremely small and seems skewed towards oldest paediatric subset. Controlled paediatric studies seem unlikely to be feasible unless cooperative, where there are many issues to be overcome. A waiver may be requested for some drugs/paediatric subsets. Extrapolation from adults/older paediatric subsets seems a feasible regulatory approach, with limited confirmatory studies (again depending upon individual drug). Whether deferral of paediatric studies is valid depends upon available data with the drug/drug class: If adult efficacy/safety data already are available or paediatric PK and safety data are available from other indications, paediatric studies could start concurrently with adults.

2.22. Discussion 5

A range of views were expressed covering:

- The possibility of a multi-company study, taking advantage of the whole population, raises the issue of whether and how regulators or academics could prioritise new medicines for trials instead of companies competing for trial subjects given the rarity of the disease.
- It was suggested that the most effective drugs could be prioritised, assuming no safety issues which make the risk/benefit profile negative. It was acknowledged that there may be limited efficacy results for these drugs in adults on which to base such a prioritisation. This issue applies not just to the paediatric population but also to the adult population.
- To avoid subsequent off label use, clinicians stressed importance of evaluating new medicines for this condition in children and could see the possibility of including children and young adults into Phase 3 adult trials. Data is needed in children above 2 years of age also.
- Appropriate doses need to be defined for the paediatric age bands. The possibility of predicting doses for children on the basis of modelling, and testing in children was discussed together with extrapolation of efficacy from adults to children. A remark was made that despite the predictions, the Relapse Rate in children is relatively small with respect to adults, time to first relapse as an endpoint may be challenging.
- See Section 1 for Post-workshop Paediatric Committee reflections.

2.23. NMO workshop exit poll results

An informal anonymous exit poll of participants present in person at NMO workshop 10 Oct 2014 was carried out. There was an overall 68% response rate (n=54) with a variable response rate amongst groups. Groups with small numbers are not illustrated. Questions and responses are summarised below.

1. Please select the category that best describes your affiliation; tick one:



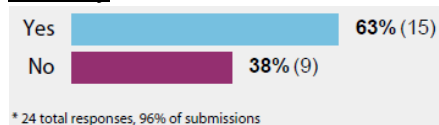
2. Is a placebo controlled trial in NMO relapse prevention currently possible (Not as add on to background immunosuppressants)?



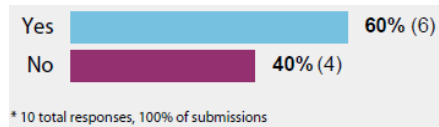
* 52 total responses, 96% of submissions

Question 2 responses by group:

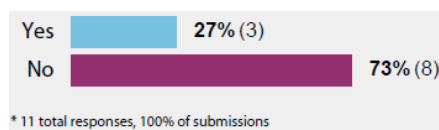
Industry:



Regulatory:



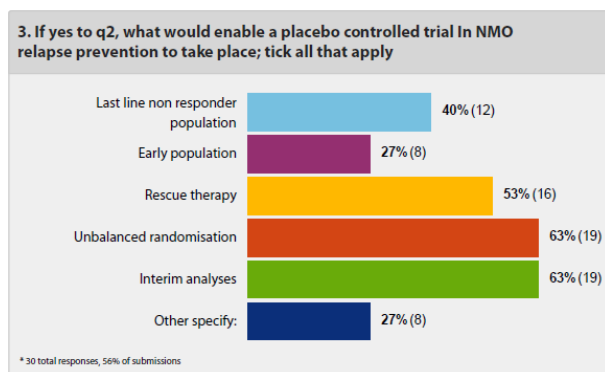
Healthcare professionals:



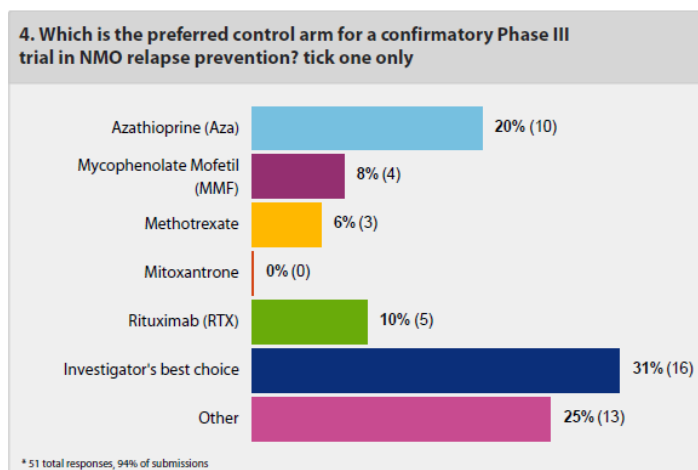
Patients:

- Very small numbers
- Majority (but not all) not in favour of placebo controlled monotherapy trials

Question 3 overall response



Question 4 Overall response:



Question 4 Healthcare professional preferred comparator:

