Workshop on multiple sclerosis
17/10/2013

Summaries of the presentations

Critical review of outcomes used in MS clinical trials

Speaker: Prof George Ebers, John Radcliffe Hospital

Multiple Sclerosis presents a difficult problem for assessing efficacy. Symptomatic therapies differs relatively little from many other chronic diseases, the determination of whether or not the natural course of the disease has been altered in the longer term has proved difficult. Although the disease is relatively predictable for groups of individuals in the longer term, there is still substantial inter-individual variation. Practically speaking it has been difficult to carry out studies which last more than 1-2 years in duration. This is from a combination of factors. However the ones that are modifiable include motivation on the parts of investigators, pharmaceutical industry and regulatory agencies.

The case of MS provides a particularly good example of the frailties of making assumptions about short term outcomes. Most MS clinical trials have been based on preventing exacerbations and improving MRI scan outcomes. These have been used for many years with little critical evaluation of their validity.

In combination with the Sylvia Lawry Centre we have assessed the short term measures used as outcomes in clinical trials and in natural history data as they relate to long term disability. Many of the results come from the natural history database established in London Ontario in the 1970s and most of these patients have reached hard long-term outcomes. The results provide a sobering critique of the way in which clinical trials have been done. The pressures to use specific trial outcomes in the short term do not seem to come from their validation. We make some suggestions about how MS trials could be executed in future with a view to determining treatment efficacy on the key outcomes about which patients, their families, third party payers are most concerned.

Disability assessment: can we combine responsiveness and clinical relevance?

Speaker: Bernard M.J. Uitdehaag, VU University Medical Center, Amsterdam, The Netherlands

A major goal in the treatment of MS is the prevention (or at least slowing down) of disability progression. This process evolves over many years. Both in trials and in clinical practice there is a need to evaluate the success or failure of interventions within a reasonable period of time. This introduces a challenge for assessing disability. Amongst other qualifications, the outcome measure should be responsive, i.e. able to detect a true change. This is related to the reliability of the outcome measure. However, a true change in a given outcome measure is not necessarily of clinical relevance, especially when the outcome measure is indirectly assessing the construct of interest.

The Kurtz's Expanded Disability Status Scale (EDSS) is the most widely used scale to assess changes in disability in MS. The disadvantages and advantages of the EDSS in assessing disability in MS are well known. Therefore the development of other measures for assessing disability in MS is advocated since these scales, if validated and justified, may replace the EDSS.

One of the important aspects of disability in MS is a affected mobility. The assessment of that construct can be approached using performance test (a timed walk test, TWT). The TWT can be performed easily and also reliably, i.e. relatively free from measurement error. This is a prerequisite for a responsive outcome measure. The question then rises whether a true change in TWT is clinically meaningful. There are indications that beyond a certain threshold, a change in TWT is clinically relevant. This encourages to further explore this approach in the development of a new outcome measure for disability in MS.

The new outcome measures in MS: Possible better ways to assess disability that overcome limitations of the EDSS

Speaker: Gilmore O'Neill, MB, MRCPI, MMSc, Neurology Clinical Development Group, Biogen Idec, Cambridge, MA, USA

MS is an inflammatory neurological disease that damages the nerve fibers and cells of the Central Nervous System (brain and spinal cord) resulting in diverse manifestations of neurological impairment and disability. The damage can occur episodically in the form of relapses (exacerbations) or steadily in the form of chronic disease progression (Primary or Secondary Progressive forms of MS).

The clinical development of medicinal products for the treatment of MS has focused mostly on treatments for reduction in the number of relapses and slowing of the effect of relapses on accumulation of disability. The main tool for measurement of treatment effects on accumulation of disability has been the Expanded Disability Status Scale (EDSS), which scores the degree of neurological impairment based on abnormalities on the neurological examination with considerable emphasis on ambulation.

The EDSS suffers from a number of well described limitations:

1. Insensitivity of EDSS in measuring clinically meaningful changes in walking @ EDSS >4.0

2. Insensitivity of EDSS in measuring other neurological systems and function

These limitations have become increasingly important as therapeutic trials attempt to address the full extent of unmet need for treatments for MS.

There have been a number of attempts to develop alternative endpoints that can measure changes in global neurological function or disease activity in Multiple Sclerosis. These include:

1. The Multiple Sclerosis Functional Composite (MSFC), using tests of short distance ambulation (Timed 25 feet walk test [T25FW]), upper extremity function (9 hole PEG test [9HPT]), and cognitive function (processing speed [PASAT]).

2. An enhanced EDSS (EDSS-plus) using the EDSS, T25FW and 9HPT

3. A clinical-radiological composite using ARR, EDSS and Magnetic Resonance imaging of the CNS to describe a patient population "free of detectable disease activity"

These alternative measures are undergoing improvements (NMSS/ NIH/ C-Path sponsored MSOAC revalidation program), implementation, and/or validation in ongoing clinical trials. The current "Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis" (Doc. Ref. CPMP/EWP/561/98 Rev. 1) advocates for the development and validation of alternative scales that may be more appropriate than the EDSS for assessing disability in MS. The revised guidance document is scheduled for finalization prior to completion of the above initiatives. It would, therefore, be important that the new guidance maintain the position of the 2006 guideline and allow for alternative measures to be used as primary efficacy measures of disability progression.

CONCLUSION:

1. EDSS has been successfully used in the development and approval of a number of DMTs for RMS

2. Nevertheless, EDSS has limitations. Alternative enhancements exist but currently lack sufficient validation data and are:

- under active use clinical trials eg EDSS plus in SPMS Tysabri

- undergoing re-development e.g MSFC @ NMSS/ C-PATH sponsored MSOAC collaboration

RECOMMENDATION:

1. Guidance should acknowledge, in more detail, the limitations of EDSS around non walking neurological function AND insensitivity to detect a clinically meaningful change in walking

2. Guidance should be open to alternative endpoints as primary efficacy outcomes pending the conclusion of multiple efforts to improve EDSS or MSFC enhancements

Approaches to advancing patient-focussed outcomes assessment in clinical trials of MS

Speaker: Prof Jeremy Hobart, Plymouth University Peninsula Schools of Medicine and Dentistry

The EMA draft guidance on the clinical investigation of new medicines for the treatment of MS highlights the importance of measuring patient focused outcomes such as disability and quality of life. This talk will: identify areas where the draft guidance can be developed further; draw on the potential contributions of other guidance documents from the field of patient-focussed outcomes assessment; and highlight evidence and aspects of measurement science that can advance the clinically meaningful

quantification of how people with MS feel and function. Recommendations for how the guidance can be revised will be made.

New perception of disability – including cognition, fatigue, pain and other impairments related to MS

Speaker: Dr Diego Cadavid, Clinical Development Group, Biogen Idec, Cambridge, MA, USA

MS is an inflammatory neurological disease that damages the nerve fibers and cells of the Central Nervous System (brain and spinal cord) resulting in diverse manifestations of neurological impairment and disability. The damage can occur episodically in the form of relapses (exacerbations) or steadily in the form of chronic disease progression (Primary or Secondary Progressive forms of MS).

The clinical development of medicinal products for the treatment of MS has focused mostly on treatments for reduction in the number of relapses and slowing of the effect of relapses on the accumulation of disability. The main tool for measurement of treatment effects on accumulation of disability has been the Expanded Disability Status Scale (EDSS), which scores the degree of neurological impairment based on abnormalities on the neurological examination with considerable emphasis on ambulation. Another tool often used but less accepted than the EDSS is the assessment of neurological function with the MS functional composite (MSFC) using tests of short distance ambulation (Timed 25 feet walk test [T25FW]), upper extremity function (9 hole PEG test [9HPT]), and cognitive function (processing speed [PASAT]).

However, there are several manifestations of MS that contribute substantially to disability and/or reduced quality of life that are NOT being measured with the EDSS or the MSFC.

These manifestations can be reported by the patient or significant others (MS symptoms) or measured using objective clinical testing (MS impairments). MS symptoms and impairments not adequately measured by the EDSS and the MSFC include loss of memory and learning, visual function, balance, sensory function, bowel and bladder function, sexual function, pain, spasticity, tremor, mood, and fatigue. Many MS patients considered to have "benign" disease have one or more of these impairments not adequately measured by the EDSS or the MSFC.

There is a need for acceptable specific endpoints to evaluate these MS symptoms and MS impairments in the context of symptomatic and disease modifying treatments. While MS symptoms are measured by patient report (e.g. pain and fatigue), MS impairments can be measured by patient, physician, and/or informant report and by objective functional tests, e.g. low contrast letter acuity for vision, and tests of learning and memory and processing speed for cognition.

The MS Guideline acknowledges the option to use various secondary efficacy endpoints based on other measures related to progression of disability. This needs broadening to allow for some measures to be Primary Efficacy Endpoints in the context of treatments for specific MS symptoms and/or MS impairments (e.g. therapies that improve cognitive function in MS patients irrespective of whether the drug impacts relapses or EDSS change).

Coordinated Efforts of the MS Community including academia, industry, patient groups, MS societies, and regulators are needed to have acceptable endpoints and instruments for assessment of treatment effects on MS symptoms and MS impairments.

Issues regarding use of placebo in MS drug trials

Speaker: Dr Peter Chin, Novartis

The draft EMA Guidance refers to placebo as a comparator for superiority trials evaluating disease modification of multiple sclerosis (MS), in addition to brief mentions in the context of acute relapses and repair of stable disability. The use of placebo-controlled trials to demonstrate efficacy and safety of new therapeutic interventions must be considered in the context of basic human rights protections. The Declaration of Helsinki establishes placebo use in studies as acceptable in diseases for which no proven treatment exists, or where the scientific methodology is compelling and necessary and where placebo-treated subjects will not be subject to any risk of serious or irreversible harm. The scientific merit of placebo-controlled study designs for evaluating disease-modifying therapies in multiple sclerosis (MS) is well established. The consensus position of international expert MS clinicians has been that long-term placebo-controlled trials are generally no longer ethically acceptable in relapsing MS, given the abundance of proven effective treatment options available. Limited use of placebo in short term studies of relapsing MS may be acceptable if the scientific value derived from the methodology offsets a minimal risk of harm to study participants receiving placebo. No proven effective therapies are available for slowing disease progression in Primary Progressive MS (PPMS) or Secondary Progressive MS (SPMS), and placebo remains a viable option in developing treatments for these forms of MS. Depending on the details of the study designs, placebo could be envisaged as a control or reference arm in evaluating treatments intended to improve apparently stable residual impairment or in acute relapses to shorten their duration, the severity of symptoms and/or to prevent permanent sequelae.

Recommendations include restricting references in the Guidance to placebo control in relapsing MS to short term use under limited circumstances. Active comparator superiority studies should be the norm for demonstrating disease modification with immunomodulators in relapsing MS. Placebo control remains appropriate in superiority trials evaluating therapies to slow or prevent progression in SPMS and PPMS. Further elaboration for evaluating treatments for acute relapses and improvement of an apparently stable residual disability would enable more informed review on the use of placebo in these contexts. The MS treatment landscape will continue to evolve and the ethics of placebo in each therapeutic context must be re-evaluated on a continuing basis.

Design strategies to minimise the use of placebo in MS clinical trials

Speaker: Dr Maria Pia Sormani, Department of Health Sciences, University of Genoa, Italy; MSOAC

Monitoring the evolution of the disease and detecting the effects of new drugs has always been very challenging in Multiple Sclerosis (MS), mainly due to the high variability of the disease. Since the first randomized clinical trial (RCT) demonstrating the efficacy of a drug in MS (1993), the number of RCTs has been exponentially increasing in MS and a standard methodology consolidated passing through phase II placebo-controlled trials, typically lasting 6 months with Magnetic Resonance Imaging (MRI)

endpoints, and ending up with phase III placebo-controlled trials lasting 1-2 years with relapse or disability progression endpoints. This process has brought to the market new drugs, and other therapies will become available in the near future. So we entered a new era of RCT in MS: since patients enrolled in trials are more and more benign and the use of placebo has become ethically questionable, new design strategies are required to handle this evolution, and a large effort is devoted to study, among other strategies to minimize the exposure to placebo, the validation of surrogate outcomes and the application of adaptive designs.

1.   Surrogate outcomes

MRI markers are widely used as primary outcomes in phase II trials. Their role as surrogate for clinical endpoints has been deeply studied and is still controversial. The possibility of their use as primary endpoints in phase III trials is now limited to specific conditions.

2.   Adaptive designs

Adaptive randomization, in which the proportion of subjects assigned to placebo changes as information is gathered, is a potential way to reduce the number of subjects receiving placebo. For such designs to be operational a relatively rapid impact of study agent must be expected and therefore MRI outcomes would be useful in such setting.

These new options will be explored in this presentation.

How to evaluate medications in MS when placebo-controlled RCTs are not feasible

Speaker: Dr Luca Massacesi, University of Florence, Italy; member of SAG-Neurology

In the last three decades, a number of medications have been proved to be effective in relapsing remitting (RR) multiple sclerosis (MS), controlling the effector phase of an autoimmune process leading to inflammation, demyelination and eventually tissue loss in the central nervous system. Administration of these drugs, now named altogether Disease Modifying Treatments (DMT), have also been approved for RRMS by EMA and by most European countries. Under this condition, in typical MS cases, prescription of these drugs cannot be postponed and therefore, in RRMS, placebo-controlled RCTs are considered unethical by most IRB/EC. However, considering that for RRMS effective treatments do already exist, any new medication whose approval is requested to EMA should prove to be superior to the existing ones and to be able to fill one or more unmet clinical need.

On the other hand,   quality of a treatment is not defined by efficacy only, being tolerability, safety, convenience of administration and cost other important issues to be considered.

In these terms the currently available MS DMT, represent an important advance for MS patients, but are far to be optimal as for most of those issues.

Then, as in the treatment of RRMS an unmet clinical need can be found in each of the above indicated issue, superiority of a new medication is desirable both in term of efficacy and in term of safety or of cost or of other characteristics, provided efficacy is at least equivalent.

If an RCT is planned for proving superiority of a medication in terms of efficacy, RCTs comparing efficacy to a comparator drug on well-established outcome measures can be easily planned using available data. Nonetheless, if a medication is supposed to be equivalent to the existing one(s) as for

efficacy, but superiority has already been evaluated as for another characteristics as tolerability/safety, convenience or cost, (even just through open trials), search for superiority of efficacy is a non-sense, but at least equivalent efficacy has to be proved anyway. In these cases, trials comparing medications whose objective is to prove non-inferiority of efficacy vs a comparator drug, is the best option. These trials can be easily designed whenever consistent data on efficacy of the comparator vs placebo are available, as it is the case of RRMS. These data are indeed needed for fulfilling the preliminary condition that makes this method reliable: a priori calculation of a clinically meaningful "non-inferiority margin", a parameter that is also needed for sample size calculation.

Patient-reported outcomes, biomarkers and novel methodologies, and their role in the development of new treatments for MS

Speaker: Dr Frank Dahlke, Novartis Pharma AG

For patient reported outcomes (PROs), the draft Guidance on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (MS) gives only non-specific guidance regarding the quality of scales recommended to support a label claim and limits itself to Quality of Life. PROs are important tools to capture patient perspective, which complement and support the meaningfulness of other outcomes. Several PROs have been validated for Multiple Sclerosis (MS) which focus on symptoms and functioning. Therefore, broader coverage of PROs in the guideline including additional guidance regarding properties of scales used should be considered.

As far as molecular biomarkers (BMs) are concerned, there is general agreement with the language of the draft Guidance given that there are no established BMs to predict therapeutic efficacy. One could however consider strengthening the potential importance of Phase 2 or 3 studies for BM validation given the size and duration of studies likely required for this purpose.

There is also general agreement with the proposed Guidance regarding imaging BM, and their potential role in MS drug development. However, it is recommended to strengthen the potential role of whole brain atrophy as a valuable marker supportive of brain tissue preservation correlating with neurological disability and sensitive to pharmacological intervention, with methodology available to apply in multi-centre Phase3 studies.

As a novel methodology to be included in the Guidance, we propose to consider Optical Coherence Tomography (OCT) as an objective, non-invasive, painless, patient-friendly technology to study the retinal nerve fibre layer (RNFL) and neurons (retinal ganglion cells) in vivo at high resolution and with high reproducibility. Changes in these anatomical structures correlate with changes of visual function, and could serve as evidence of tissue protective effects in exploratory studies and/or support claims on preservation of neuronal tissue.

Optical coherence tomography: A role in monitoring multiple sclerosis

Speaker: Dr. Celia Oreja-Guevara

Optical coherence tomography (OCT) is a non-invasive, accurate and simple high resolution technique to quantify the thickness of retinal nerve fiber layer (RNFL). It is capable of measuring the unmyelinated axons of the retinal ganglion cells as they converge on the optic disc to convey the visual information from the retina to the lateral geniculate nucleus. Initial studies demonstrated OCT usefulness to detect retinal axonal loss following an acute episode of optic neuritis. Several studies have also demonstrated the usefulness of OCT to monitor axonal loss in patients with MS. In MS, axonal loss occurs not only after each episode of ON, in correlation to visual outcomes, but it also occurs even in the absence of inflammatory episodes. The degree of axonal loss is correlated with the duration of the disease, with more thinning as the disease advances and in progressive forms.

The use of OCT to quantify axonal loss in the RNFL is a promising tool to evaluate disease progression in MS and ON patients. OCT measurements seem to correlate with MRI measured brain atrophy. OCT could provide an easily quantified and highly reproducible method in clinical trials to detect treatment effects and to monitor the efficacy of new neuroprotective therapies in MS.

Assessing benefit-risk profile of novel immunomodulatory drugs with significant efficacy but with potential risks. What data should be presented at marketing-authorisation application?

Speaker: Michael Panzara, Group VP, Therapeutic Area Head for MS and Neurology, Genzyme, a Sanofi Company

Multiple Sclerosis (MS) is a serious and disabling disease where a significant unmet need exists to develop therapies that halt disease progression and restore lost function. From the earliest stages, subclinical immune disease activity is leading to loss of neurons. Ongoing disease activity at any stage in both treatment naive and patients on treatment, impacts daily lives, predicts poor prognosis and increases risk for permanent disability. This has led to an evolving treatment paradigm where immunomodulatory treatments with high efficacy are given at the earliest stage of the disease to prevent irreversible neurological damage, regardless of prior treatment history. However, concern over the potential for rare and sometimes serious adverse events when potent immunomodulatory treatments are used has led to an increasingly cautious approach to clinical development and restrictions limiting use to later stages of the disease. Although well meaning, such an approach has the potential to impede the development of novel therapeutics without enhancing benefit risk equation, restricting potent immunomodulators from those early in disease course who are most likely to benefit.

This presentation will use case studies to discuss the development of novel immunomodulatory treatments in the context of the proposed guidance, providing recommendations as to the data needed to assess benefit risk profile at the time of MAA.

The proposed 'two-step approach' for MS treatments with a significant effect on immunity

Speaker: Hideki Garren, MD, PhD (F.Hoffmann- la Roche Ltd. on behalf of EFPIA)

The draft guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (MS) proposes a two-step approach for the conduct of clinical studies for compounds with a profound effect on the immune system. In short, the two-step approach consists of a first step where the compound is evaluated in patients with insufficient response to first line treatment, followed by a second step where the compound is studied in a broader population.

The main recommendation made in this presentation is to have a parallel approach rather than a two-step approach. A key rationale to defend a parallel approach is the fact that the two-step approach could unnecessarily delay access to promising new medicinal products for patients up to 5 years. Furthermore, the two-step approach can lead to a situation where compounds may never be studied in the earlier, more inflammatory patient group (where it may have more benefit), when the compound does not 'pass' the first step of studying the compound in patients insufficiently responsive to 1st line treatment. Besides this, a two-step approach would be redundant, where anticipated risks can be managed via appropriate risk mitigation procedures in the clinical trials setting.

During the presentation, these rationales will be further explained and Dr. Garren will elaborate on the several challenges with defining partially responsive patients and the compound definition.

Current treatment guidelines for relapsing MS and the 'two-step approach' for disease-modifying therapy

Speaker: Klaus Schmierer, Blizard Institute, Barts and The London School of Medicine

This talk will challenge the rationale underlying the EMA's 'two step approach' in MS disease modifying therapy (DMT) on four grounds: (i) prediction of disability, (ii) efficacy of DMT, (iii) side effects of DMT and (iv) cost of DMT. With emphasis on the practise in the UK the significant overlap between the EMA's 'two step approach' and MS treatment guidelines that are primarily concerned with cost effectiveness will be explored.

Changing population in MS studies & concept of insufficient treatment response

Speaker: Dr Gordon Francis, Novartis

Differences in patient populations of more recent MS studies that impact outcomes include lower disease activity prior to entry and the prior use of disease-modifying therapy. Definitions of endpoints and methods of analysis of key endpoints have also changed. The changed population characteristics can lead to "floor-effect" particularly on relapses, resulting in higher risk of imprecision of treatment effect estimate, rendering interpretation of the clinical relevance of absolute and relative treatment effects more difficult. These changes also render comparison with historical data, including potential

virtual placebo, problematic. To address these issues, recommendations include requiring sufficiently sized (powered) studies, with replication, to have confidence in the effect size detected; direct comparative studies, or a consideration of modelling patient-level data to provide indirect comparisons that adjust for population and study differences.

Specific to SPMS, the draft Guidance recommends only including non-relapsing SPMS in studies in order to better assess true (i.e. non-relapse related) disability progression. EFPIA does not agree, given that relapsing SPMS is a part of the spectrum of SPMS and confounding related to relapses can be addressed by randomization and appropriate analyses.

The draft Guidance uses terms such as "insufficient(ly) responsive" to treatment to define patients to be included in studies of potentially potent immunosuppressive medications. However, there is no clarity around these definitions, or an indication of whether this would vary by disease stage. Given the increasing pool of "first-line" therapies, it is also not clear if patients must be insufficiently responsive to one, several or all before becoming eligible for escalation, either in clinical trials or in post-approval setting. There is no consensus regarding what would be the minimal efficacy criteria to define insufficient response, nor consensus on how safety, tolerability or patient preferences would be incorporated (other than arbitrary decisions, absent supporting data). Unless a consensus could be developed, it is recommended to remove generic terminology about treatment unresponsiveness from Guidance document as it is not viewed as being helpful in development of therapies for MS patients. Additionally, CHMP/EMA should be encouraged to clearly define, in conjunction with academia and industry, criteria for 1st-line and 2nd-line therapies to avoid post-facto sub-group definitions.

When considering benefit-risk (BR) for products, either in development or labelling, the focus, appropriately, is on patient safety, but consideration must also be given to reduced efficacy if patients are required to use (potentially) less effective therapies based on hypothetical (or even demonstrated) safety issues. Future relapses, disability progression and loss of brain tissue are also of concern to MS patients, just as are adverse events. Patient input on risk tolerance should also be considered by regulators when study data is reviewed and label language is being drafted.

Data from animals, pharmacodynamic studies and related class compounds are helpful but themselves have limitations and should not alone determine in which (sub)-population a compound should be investigated in MS. BR evolves with each stage of development and should appropriately weigh the cost of reduced efficacy vs. risks so as not to unnecessarily restrict the patient population to be studied or patients' ability to access an effective therapy.

Clinical-development issues in progressive MS

Speaker: Volker Knappertz, Vice President, Head of Global Clinical Development, Multiple Sclerosis, Teva Pharmaceuticals R&D

PPMS patients are generally older than RRMS patients at diagnosis, and therefore are more likely to have co-morbidities, inevitably complicating trial conduct, recruitment and interpretation. PPMS patients generally have acquired higher levels of disability, which may limit their adherence to visits in demanding clinical trials. Additionally the window of EDSS scores to study is narrowed. Due to metric and biological reasons the upper end of the EDSS range needs to be limited and the lower bound needs to be sufficiently high to be consistent with the diagnosis of progressive MS, leading to ranges from 2.5-6.5 with limitations and uncertainty of appropriateness at both ends.

Modest slowing of disability progression is unlikely to be apparent to the trial participant or investigator, and waiting for definitive worsening on hard disability outcomes may require several years of study. Therefore the progression on trial needs to be adequate evidence and buttressed with long-term outcome data as well as biomarkers consistent with alleviating neurodegeneration. Retention on clinical trials will be more challenging with increasing usage of off label treatments for PMS in several regions. Large numbers of patients and long periods of study are required to establish a treatment effect in this substantially smaller PPMS population compared to RRMS and SPMS, posing significant challenges to sponsors and trialists. There is currently no path of orphan drug designation established and this proposal been declined in the past, citing PPMS as a spectrum of the MS disorders by regulators.

The PPMS diagnosis requires substantial neurological expertise. The 2010 McDonald Criteria require two out of three criteria, ie lesions on brain MRI, spinal MRI and CSF abnormalities to be fulfilled. Therefore, inclusion criteria need to be closely monitored, CSF IgG index or oligoclonal bands need careful consideration, albeit their usage varies greatly by regions and centers. The complicating aspect is that these have predictive value for progression propensity. Careful balance between expanded age and EDSS inclusions needs to be taken as these may create skewed distributions and   imbalances in higher age and disability strata, lowering assay sensitivity. On the other end of the spectrum patient selection at the early stage of the disease the risk of misclassification is higher. Current tools to measure progression of disability are suboptimal (e.g., EDSS is an ordinal scale, progression is different by level for both time and level of disability). Therefore, additional measure of progression including the 25FTTW, The 9-HPT, and the SDMT will need consideration for incorporation into the progression criteria. Other clinical disability scales remain unvalidated and wanting. Currently available biomarkers face similar issues rendering them unsuitable as primary trial endpoints as outcome measures. Therefore, the EDSS progression with additional allowance for the individual MSFC component's (replacing the PASAT with the SDMT) progression to contribute to progression is the proposed PEP for two year confirmatory trials in progressive MS. The treatment effects for all DMTs currently tested vary between RRMS and PPMS, with effects in PPMS observed only in subgroups usually with demonstrable acute inflammatory activity by either MRI or clinically. Potential options to explore the disease include advanced MRI techniques (MTR, DTI) OCT, as well as neurophysiological measures. Monitoring of neurofilament levels in CSF deserves exploration as a treatment response marker for neuronal and axonal degeneration. Positive findings on either of these evolving biomarkers of degeneration should be viewed supportive of any clinical disability progression effects.

The similarities between patients that have RRMS and progress to SPMS to patients with PPMS has prompted key nosologists in the MS field to assess these entities as phenotypic variants of the same pathophysiological process. A pointed statement describing this is: "PPMS is RRMS which skipped the relapsing phase".

The evidence supporting this position ranges from clinical progression features, epidemiology, the age of onset of the progression phase, genomics, genetics in familial forms, neuropathological features and MRI findings on brain atrophy rates and lesion distribution and load, all found to be similar between these populations when adjusted for age or degree of disability. The unmet medical need and the failure of current RRMS DMTs to mitigate progressive MS (PMS) is to address the steady progression of disability with or without additional deterioration as a result of acute superimposed relapses. Prevention or delaying the accumulation of disability should be the goal of the treatment. An effect on superimposed relapses without an accompanying effect on disability is less important in PMS than in RRMS. Therefore, to evaluate the efficacy of a therapeutic product against disability progression in PPMS and SPMS (PMS), it is recommended to target predominantly PMS patients without relapses in order to exclude possible effects on disability related to effects on relapse activity in large-scale, adequately powered and of adequate duration, placebo controlled, parallel group trials. This approach

will allow for the establishment of efficacy on the progressive aspects of the disease and sensitivity analyses across various clinical, MRI, and biomarker aspects of a large PMS Phase 3 trial population will enable an understanding of the contribution of the main effects, including a sensitivity analysis by Lublin-Reingold phenotypes.