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Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis

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This guideline replaces the guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis (CPMP/EWP/561/98, Rev.1).

Comments should be provided using this template. The completed comments form should be sent to CNSWPSecretariat@ema.europa.eu

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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Executive summary

The present document is a general guidance on the development for medicinal products for the treatment of Multiple Sclerosis (MS) and should be read in conjunction with other EMA and ICH guidelines, which may apply to these conditions and patient populations.

The goal of treatment determines the type of study designs, populations, primary endpoints and duration of the trials. Emphasis has been put on treatments that modify the natural course of the disease which require long term superiority trials with the relapse rate and disability as the most important endpoints. For products with an anticipated profound effect on the immune system and thus potential serious safety a two step procedure is foreseen. Firstly, such products should be evaluated in comparative superiority study in patients with insufficient responsive to first line treatment. If the safety profile is judged to be acceptable, efficacy studies may be extended to a broader multiple sclerosis population.

With respect to children, the generation of specific data is expected. Depending on the mechanism of action and the expected safety profile, this might be done by performing clinical trials tailored to children, by incorporating adolescent MS patients into the adult trials and/or by extrapolating efficacy observed in adult MS patients to children, provided the dose and short term safety is established and the long term safety is evaluated.

1. Introduction (background)

Multiple Sclerosis is a common neurological disease affecting more than 1 million people worldwide. Its prevalence rate varies between races and region, ranging from more than 100 per 100,000 in Northern and Central Europe to 50 per 100,000 in Southern Europe. The incidence appears to increase.

MS is an inflammatory condition that damages the myelin of the Central Nervous System (CNS) and causes neurological impairment and severe disability.

The aetiology of MS remains unknown. It is generally assumed that MS is mediated by some kind of autoimmune process triggered by an infection, superimposed upon a genetic predisposition.

Eighty two to 85 % of all patients present with relapsing-remitting (RR) MS, which is characterised by unpredictable acute episodes of neurological dysfunction named relapses, followed by variable recovery and periods of clinical stability. Within ten years more than 50% of patients who presented with a RR form eventually develop sustained deterioration with or without relapses superimposed; this form is called the secondary progressive variety of MS (SPMS). The term relapsing MS (RMS) applies to those patients either with a RRMS form or a SPMS form that are suffering relapses. Patients with RMS, in spite of suffering from different MS forms, constitute a common target for current treatments.

Around 15% of patients develop a sustained deterioration of their neurological function from the beginning; i.e. primary progressive MS (PPMS). Some patients who begin with a progressive deterioration may experience relapses with time and this form is called progressive relapsing MS. Besides these main types of disease, the benign variety of MS refers to a RR form with few relapses and no significant disability after several years of evolution. Conversely, the term malignant MS applies to a very aggressive variety leading to severe disability or death in a few years after the onset of the disease.

The term clinically isolated syndrome (CIS) refers to patients with a first clinical event that can be attributed to a demyelinating event that does not comply with the diagnostic criteria for definite MS i.e. dissemination of demyelinating events in time and place either clinically or radiographically[3]

Pathophysiological processes involve acute inflammatory focal lesions, gliosis, demyelination, impaired remyelination, axonal loss and neuronal loss which occurs at all stages of the disease. The relative contribution of these processes changes during the course of the disease. Relapses are considered the clinical expression of acute inflammatory focal lesions whereas progression is more associated with demyelination, impaired remyelination, axonal loss and neuronal loss. In primary progressive multiple sclerosis the inflammation is cortical and more diffuse.

The current therapeutic approach involves symptomatic treatment, treatment of acute relapses, and disease modifying therapies.

Symptomatic treatment refers to all therapies applied to improve symptoms and complications caused by the disease e.g. fatigue, spasticity, ataxia, walking disability, weakness, bladder and bowel disturbances among others. In general these treatments are non specific. More MS specific treatments are those that intend to facilitate remyelination or facilitate axonal conductivity.

The standard of care for acute relapses is methylprednisolone. Methylprednisolone does shorten the duration of relapses but has no influence on the sequel of the relapse. Plasmapherese is rarely used.

Treatment aimed to modify the course of the disease includes immunomodulators (betaferons glatiramer acetate, monoclonal antibodies), α4β-integrin antagonists, sphingosine analogues (fingolimod), immunosuppressants and cytotoxic agents. These therapies aim to prevent relapses and ultimately to diminish the accumulation of disability. Due to the risk of opportunistic infections and secondary malignancies, many of these are second line options.

2. Scope

This Guideline is intended to provide guidance for the evaluation of drugs for the treatment of multiple sclerosis. The guideline primarily focuses on treatments aimed to modify disease progression. In addition some remarks are made concerning the treatment of relapses, repair and restoration of functioning. Products aimed to treat complications of the neurological dysfunction are out of the scope of this guidance.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles (4) and part of the Annex I to Directive 2001/83 (as amended) and relevant CHMP and ICH guidelines, among them in particular:

- Statistical principles for clinical trials (CPMP/ICH/363/96, ICH E9)
- Note for guidance on population exposure: extent of population exposure to assess clinical safety (CPMP/ICH/375/95, ICH E1)
- Pharmacokinetic studies in man (Eudralex vol 3C C3A)
- Dose response information to support drug registration (CPMP/ICH/378/95, ICH E4)
- Note for guidance on clinical investigation of drug interactions (CPMP/EWP/560/95)
- Choice of control group in clinical trials (CPMP/ICH/364/96, ICH E 10)
- Guideline on missing data in confirmatory clinical trials (CPMP/EWP/177/99)

[3] Polman C et al, Diagnostic Criteria for Multiple sclerosis: 2010 Revisions to the McDonald Criteria, Ann Neurol 2011; 69:292-302

- Reflection paper on the extrapolation of results from clinical studies conducted outside Europe to the EU population (EMEA/CHMP/EWP/692702/2008)
- Note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99, ICH E11)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005)
- Guideline on similar biological medicinal products containing interferon beta (EMA/CHMP/BMWP/652000/2010)

4. Specific considerations when developing products for the treatment of multiple sclerosis

Treatments of MS may have different goals with different clinical development plans and clinical trial designs:

A) Treatment of acute relapses to shorten their duration and/or severity of symptoms and/or preventing their sequelae.

B) Modification of the natural history of the disease. This includes:

- Preventing or delaying the accumulation of disability.
- Preventing or modifying relapses.

C) Improvement of an apparently stable residual disability

4.1. Treatments for acute relapses

Neurological impairment due to a relapse may improve either completely or partially within weeks or few months. Regarding a specific attack, the prediction of the course and degree of functional outcome is not possible. Therefore, parallel controlled clinical trials are mandatory to assess the benefit of any new therapy aimed to treat acute relapses.

4.2. Treatments intended to modify the natural course of the disease

It is important to differentiate between the clinical patterns of the disease: relapsing remitting multiple sclerosis, secondary progressive multiple sclerosis with and without relapsing activity and primary progressive multiple sclerosis (see introduction). Although these patterns are primary descriptive, some differences in histopathology and Magnetic Resonance Imaging (MRI) activity exists.

4.2.1. Relapsing multiple sclerosis

The term relapsing MS includes 1) patients with RRMS, 2) patients with SPMS and superimposed relapses and 3) patients with clinically isolated syndromes (CIS) who show dissemination of lesions in time and space on MRI scans according to the revised McDonald's criteria.

Prevention and/or modification of relapse features as well as prevention or delay of the accumulation of disability are meaningful goals in the treatment of relapsing multiple sclerosis. Some of the currently approved therapies have demonstrated a favourable effect on the rate and severity of relapses as well as an effect on short-term (a few years) progression of disability. However, it remains surprisingly

difficult to relate relapses prevention to prevention of disability. Therefore a claim of an effect on disability can not be claimed when not evaluated separately. For this large-scale long-term parallel group trials will be required to establish clinically relevant treatment differences on disease progression. Depending on the population studied, such study may need to last 3 years.

In recent clinical studies, the relapse rates in the studied patient population are less as compared to the population studied in earlier studies in multiple sclerosis. Hence the clinical relevance of a statistically significant treatment difference in the relapse rate might be difficult to evaluate. Therefore a justification of such benefit should be provided (see section 6).

In the development of new compounds intended to modify the natural course of multiple sclerosis, the anticipated benefit-risk profile needs to be taken into consideration. The reason is that so far the more effective agents also have an increased risk of opportunistic infections and malignancies, among other safety issues. Hence, the anticipated benefit-risk profile should be weighed against the benign/malignant course of multiple sclerosis of a patient and the life expectancy of multiple sclerosis. Before clinical data are available, this anticipated benefit-risk profile could be based on, among others, studies in animals, pharmacodynamic studies, use of the product in other indications or known mechanism of action. Based on this, the population included in the planned studies should be defined.

For compounds with a new mechanism of action, efficacy should be established by means of randomised double-blind controlled parallel group superiority trials. Superiority needs to be shown versus placebo or first line treatment, depending on the anticipated benefit-risk profile.

New compounds with an anticipated modest efficacy and mild safety profile will be used in patients with early multiple sclerosis and/or a benign course of their disease, if treatment is deemed indicated. For these products, randomised double-blind controlled trials are needed showing superiority versus placebo or active comparator (i.e. betaferons, glatiramer). Non-inferiority trials versus these first line products, in the absence of a placebo are insufficient, as apparent efficacy could be explained by the regression to the mean, a real placebo effect, as well as by the natural course of the disease. Differences from placebo are not consistent across trials and the sensitivity of the available scales to measure progression of disability does not assure the ability to detect clinically relevant differences.

Add-on designs as an alternative study design may be considered. However, the risk with regards to additive immunosuppression effect needs to be taken into account. Moreover, this would be reflected in the indication.

For compounds with an anticipated profound effect on the immune system and thus potential serious safety concerns these risks may be outweighed by a larger effect. Usually these products are restricted to patients partly responsive to first line treatment and/or an (anticipated) rapid progression of their disease. Therefore a two step approach is recommended. As a first step, the product should be evaluated in a comparative superiority study in patients insufficient responsive to first line treatment and/or an (anticipated) rapid progression of their disease. For these compounds, an add-on design is not recommended as it is likely that combination therapy will have an additive effect with respect to safety. As a second step, if the safety has raised no major concern, superiority studies versus first line treatment /placebo may be considered to evaluate efficacy in a broader multiple sclerosis population.

For biosimilar products, reference is made to the relevant guidelines (see section 3).

4.2.1.1. Clinically Isolated Syndrome (CIS)

For those products that do have CIS in the indication, this is restricted to patients with a clinically isolated syndrome at risk for definite multiple sclerosis based on the MRI picture. As these patients nowadays would comply with the revised diagnostic criteria for MS (Mc Donald's criteria 2010), this

indication is covered by an approval for the treatment of relapsing RMS. The inclusion of these patients in the development of a product for an indication for MS is welcomed. The usefulness of developing products for patients with an isolated clinically demyelinating event without MRI signs complying with the diagnostic criteria for MS is doubtful, however and if intended, discussion at a Scientific Advice is recommended.

4.2.2. Secondary progressive multiple sclerosis (SPMS)

Patients with SPMS suffer from steady progression of disability with or without additional deterioration as a result of acute relapses superimposed. 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 than in RRMS.

Therefore, to evaluate the efficacy of a product against disability progression in SPMS, it is recommended to target only SPMS patients without relapses in order to exclude possible effects on disability related to effects on relapse activity.

As progression to disability may take years, large-scale long-term placebo controlled parallel group trials are required.

4.2.3. Primary progressive multiple sclerosis (PPMS)

So far, clinical trials evaluating the efficacy of new agents in primary progressive multiple sclerosis have not been successful in showing efficacy. Randomised double blind placebo controlled clinical trials will be necessary in order to assess the efficacy of any new treatment in primary progressive multiple sclerosis.

4.3. Treatments intended to improve apparently stable residual impairment

Improvement of a fixed neurological impairment is a worthwhile treatment goal on its own in multiple sclerosis. Products that may potentially facilitate remyelination or improve nerve conduction are helpful.

In both situations randomised double blind placebo controlled parallel group trials will be needed for establishing efficacy. For symptomatic treatment the improvement should be supported by a clinical meaningful effect on activities on daily life. Maintenance of treatment effect should be clear and in case of products improving nerve conduction, overstimulation should be excluded.

4.4. Combination therapy

The possibility of combination therapies may be a suitable approach.

When combining therapies several aspects should be considered. Firstly, it is possible that combination of useful immunomodulators does not improve efficacy or even may show less efficacy due to some antagonisms in their respective actions. Hence it is essential to know when combining immunomodulators/-suppressants whether under monotherapy the same efficacy can not be obtained.

The possible risk of a too potent suppression of the immune system should be considered with respect to, e.g. infectious processes at the Central Nervous System, inhibition of existing remyelinisation, secondary malignancies (see section 4.2.1).

The combination of disease-modifying and symptomatic treatment has a clear rationale. However, from a study design perspective it may interfere with the interpretation of study results as an observed

effect may be attributed to both treatments whereas the contribution of the different treatments may not be disentangled.

5. Criteria for assessment of efficacy in confirmatory trials

5.1. Treatments for acute relapses

Duration and severity of relapses and overall recovery or prevention of their sequelae are relevant parameters.

If, for a test drug an effect on the duration, severity and/or recovery from a relapse is claimed, this claim should be based on clinical trials with methylprednisolone as a positive control and a placebo arm for the internal validation of the study. Such study should include early escape conditions to allow rescue treatment when the patient fails to improve or worsens. Patients should be followed for an appropriate time (e.g. at least 6 months) after each relapse to be sure that the degree of recovery after the relapse is well assessed.

Alternative study designs may be a superiority trial versus methylprednisolone, or a placebo controlled trial in the add-on setting i.e. on top of corticosteroids. As there is no consensus concerning the corticosteroid dosage regimen in context of a clinical trial, the corticosteroid regimen should be standardized.

The impact of those acute treatments on the subsequent course of the disease (rate and severity of further relapses, progression of disability, even change from relapsing remitting into SPMS) is also relevant.

5.2. Treatments aiming to modify the natural course of the disease

5.2.1. Primary efficacy parameters

A distinction should be made between accumulation of disability in relation to relapses in RRMS and progression of disability in SPMS or in PPMS.

The primary efficacy parameter in confirmatory trials in SPMS and in PPMS should be a clinically measured prevention or delay of the disability progression.

In patients with RRMS or SPMS with superimposed relapses (RMS), the primary efficacy parameter may be the relapse rate although it cannot be taken as a surrogate for disease progression and this would be expressed accordingly in the SmPC. Moreover, progression of disability should be evaluated and worsening of disability should be reasonably excluded by means of adequately powered long-term studies.

It would be highly desirable also to evaluate if the effect on progression is maintained on a long-term basis.

5.2.2. Secondary efficacy endpoints

- Disability. In studies where it is not the primary variable, it is a very important secondary endpoint that should be evaluated.
- Relapses. Recommended parameters are the rate of relapses (in studies where it is not the primary efficacy parameter), frequency of moderate/severe relapses, proportion of patients

free from relapses at a given time, time to first relapse, proportion of subjects receiving rescue therapy, number of relapses.

- MRI derived parameters.
- Absence of disease activity i.e. absence of relapse and MRI-activity
- Other measures related to progression of disability supplementary to the measure chosen such as the primary variable (e.g. neurological rating scales, measures of cognitive impairment, fatigue scales, ambulatory index.

6. Methods to assess efficacy

6.1. Progression of disability

The Kurtz's Expanded Disability Status Scale (EDSS) is the most widely used and known scale to assess changes in disability in MS.

The disadvantages and advantages of the EDSS in assessing disability in MS are well known. Therefore, on the one hand, the development of alternative scales for assessing disability in MS is advocated since these scales, if validated and justified, may be more appropriate than the EDSS. On the other hand, the EDSS should still be used in order to facilitate comparisons with other studies.

As the EDSS has a limited inter and intra-observer reliability, all possible actions intended to increase reliability of the scale should be adopted: training of observers, same physician evaluating the patient throughout the trial, standardised times and schedules for assessments, standardised protocols for neurological examination, measured distances for assessments of mobility and definitions of all the terms used. The mean change in score from the baseline is not an appropriate efficacy parameter. Based on EDSS scores, treatment failure or progression should be predefined e.g. as the achievement of a specified degree of disability or of a sustained worsening of relevant magnitude (1 point when EDSS scores ≤ 5.5; 0.5 points if baseline score is > 5.5). Acceptable efficacy parameters endpoints are the time to reach progression or the proportion of individuals who have shown progression at a pre-specified time.

Accurate and reliable definition of sustained worsening is important and should include two consecutive examinations carried out by the same physician at least 6 months apart.

As a supportive parameter, disability can also be expressed by summary measures obtained from serial measures at scheduled visits, indicating the degree of disability experienced by the patient during a period of time, disregarding whether it is in relation to relapses or not. It is recognised that the EDSS does not adequately assess upper limb function and cognitive impairment and the use of specific methods could be useful. In this context, additional neurological rating scales, quantitative neuron-performance tests (e.g. MSFC) or patient and neurologist global opinion may be used as secondary measurements of disability.

6.2. Relapses

The annualised relapse rate is an acceptable parameter to assess relapses. The definition a priori of responders in terms of absence of relapses is recommended.

Identification of a relapse may be difficult as patients frequently suffer from pseudo-exacerbations caused by infection, heat, or stress. An accurate definition of relapse (their occurrence, time of beginning, time of ending, minimum duration to qualify as a relapse, maximum time elapsed between two symptoms to qualify as a single relapse, severity) should be included in clinical trials. Identification of relapses should be blinded to therapy. The use of corticosteroids (or other concomitant therapies)

for the treatment of acute relapses that may occur throughout the trial should be carefully standardised.

Even if an effect on relapses may be shown within one year, a maintained effect on relapses should be demonstrated at least during two years. Time to next (second relapse) is not considered a good efficacy parameter.

The analysis model should be specified in the study protocol and ensure type-1 error is controlled including reasonable assumptions regarding the variance. Furthermore, the impact of premature withdrawal needs to be explored based on reasonable assumptions of the expected relapse rate in the missing observation time. A sensitivity analysis is recommended. Reference is made to the CHMP guideline on missing data (see section 3).

6.3. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a useful tool for monitoring CNS lesions in MS.

Different MRI derived parameters have been related to clinical activity, e.g. gadolinium-enhancing lesions or new/enlarging T2 lesions have been related to relapses.

The possible correlation between MRI parameters and long-term clinical outcomes is of utmost importance and several measures have been studied such as total lesion load (on T2 weighted images), chronic T1 weighted hypointensity (chronic "black holes") or several brain atrophy measures that have been related to tissue loss.

In non-relapsing SPMS and PPMS, measures of CNS atrophy including grey and white matter volumes, and new MRI techniques (vide infra) may be particularly useful.

So far, MRI measurements have not been proven to be a reasonably validated surrogate endpoint of the clinical outcomes and are, therefore, not acceptable as a primary endpoint in pivotal studies. In exploratory trials, however, changes in MRI findings may be used as a first indication of dealing with a potentially clinically effective product. However, MRI criteria used so far dominantly focused on the inflammation component. Potential useful treatments may be missed by screening potential agents in MS on MRI criteria only. This especially may apply for progressive multiple sclerosis.

All possible actions should be taken to ensure high quality MRI data and maximum reliability of measurements. Updated recommendations on appropriate technical facilities and standardised procedures and training should be followed.

Reading of MRI images should be central and blinded.

6.4. Quality of Life (QoL)

Few data are available on validation of specific instruments for QoL in patients suffering MS. If evaluation of QoL in MS is considered, reliable and validated scales should be used. Results, if considered relevant, may be mentioned in section 5.1 of the SmPC.

7. Selection of patients

7.1. Diagnostic criteria

Nowadays, the revised McDonald's criteria (2010), which incorporate MRI criteria for dissemination in time and place, are widely accepted. As a consequence the diagnosis can be made earlier which has drastically changed the MS population included in the clinical trials.

7.2. Type of patients

Patients in trials may be treatment naïve patients, patients who switch for reasons other than lack of efficacy, patients with suboptimal response to previous treatment. Depending on the purpose of the trial and anticipated benefit-risk profile of the investigational agent different patient population, should be selected a priori.

For disease modifying compounds with an anticipated modest efficacy and mild safety profile, patients with early multiple sclerosis and/or a benign course of their disease may be incorporated in the trial. For compounds with an anticipated profound effect on immune surveillance patients unresponsive to first line treatment and/or an (anticipated) rapid progression of their disease are the appropriate patient population. Depending on the efficacy and safety observed further studies in naïve patients, patients who switch for reasons other than lack of efficacy may be considered (see section 4.2.1).

Within each clinical form of the disease, relapse activity and severity of disability (e.g. defined according to EDSS score of < 3.5, 4-6 and > 6.5) as well as identifiable risk factors for high rate of relapses are important characteristics to define a priori subgroups of patients.

In trials intended to evaluate the relapse rate, it is recommended not to include subjects with SPMS and superimposed relapses as this might complicate trial design and hamper the interpretation of the effect on relapses and disability.

For treatments aimed to improve a fixed neurological impairment, facilitate remyelination or improve axonal conductivity the patient population may be broader as long as it can reasonable be excluded that there is no interaction with respect to the course of multiple sclerosis.

Currently biomarkers are evaluated that may identify subgroups at risk for rapid disease progression and/or patients that benefit more form treatment than others. Treatment adapted to patient characteristics is encouraged but will need justification and will be reflected in the indication.

7.3. Special populations

Paediatric patient population

The incidence of RRMS below the age of 16 years is low. Around 3-5% of MS patients experience their first MS attack before the age of 16 years and less than 1% before the age of 10 years. Other forms of MS, such as PPMS and SPMS are extremely rare in the paediatric population.

The clinical manifestations of paediatric-onset MS resembles that of adult-onset RRMS, However compared to adult onset RRMS, especially younger children, appear to have more frequent relapses, earlier cognitive deficits, restore better from relapses and have a slower disease progression. Differential diagnosis from Acute Disseminated Encephalomyelitis (ADEM) might be challenging.

Clinical trials in children /adolescents with RRMS are difficult to conduct because of the low number of paediatric MS patients. Nevertheless, the generation of specific data is expected. This might be done by performing clinical trials tailored to children, by incorporating adolescent MS patients into the adult trials and/or by extrapolating efficacy observed in adult MS patients to children provided the dose and short term safety is established and the long term safety is evaluated.

Considering the life-long treatment the generation of longer term safety data concerning mental, cognitive, growth and sexual development are needed. Patients should preferably be included in registries to monitor long term safety and efficacy.

8. Strategy and design of clinical trials

8.1. Pharmacodynamics

The potential mechanism of action should be explored and discussed in relation to data obtained in relevant animal models (e.g. experimental autoimmune encephalomyelitis) and to changes in biological parameters seen in patients or healthy volunteers.

When a combination therapy is pursued, hypothesis on synergism and lack of antagonism should be described and evaluated in relevant models whenever possible.

Study of changes in biological parameters and occurrence of side effects in patients or healthy volunteers, if available and pertinent, may guide the dosage and dose regimen in later studies as well as support hypothesis about useful combination therapy.

8.2. Pharmacokinetics

Pharmacokinetics of the drug should be thoroughly investigated in accordance with relevant guidelines.

8.3. Interactions

Data on pharmacodynamic interactions with other treatments of the disease are important. The possible interaction with the courses of corticosteroids to treat relapses should be addressed. Human studies of pharmacodynamic interaction between putative combinations are necessary prior to conduct clinical investigation of such combinations.

Pharmacokinetic interactions should be investigated in accordance with relevant guidelines.

8.4. Exploratory trials

Characteristics of patients to be included may vary according to the proposed mechanism of action and goal of the treatment. However, to maximise possible treatment contrast, it seems reasonable to choose patients with predictors of high clinical activity and with only mild/moderate disability.

In exploratory trials in RMS, the use of MRI derived parameters, as the main endpoint, for assessing preliminary efficacy, dose-selection is acceptable (see section 6.3). Relapses and other clinically meaningful outcomes should also be evaluated.

Depending on the proposed mechanism of action and stage of the process where the new treatment is proposed to act, lack of MRI changes may not be indicative of lack of clinical activity. In SPMS or PPMS, MRI might be less helpful and disability should be assessed in addition to supportive MRI data. A longer duration of the trial will be needed.

The search for valid biomarkers of disease activity, therapeutic activity and long-term prognosis is important. Useful markers may improve the efficiency of confirmatory trials with respect to patient selection, dose optimisation, early and late identification of failing patients, etc. This may refer to, but is not restricted to, putative markers of immune activity, remyelinisation and pharmacogenomics. It could be recommended as an integrated part of the drug development programme. When combination therapy is planned, the assessment of general clinical safety and the absence of worsening MS should be addressed at this phase.

8.5. Confirmatory trials

The annual relapse rate in RRMS is usually low and, in general, progression of disability takes years.

Consequently, confirmatory studies with products intended to modify the course of the disease should be large scale and long enough to have a substantial proportion of patients suffering relapses or showing progression of disability. Two years is considered the minimum duration to demonstrate efficacy.

For compounds with a new mechanism of action efficacy should be established by means of randomised double blind controlled superiority trials. Superiority might be shown against placebo or first line treatment. Non-inferiority trials in absence of placebo are insufficient as the only proof of efficacy. A non-inferiority design will raise difficulties as the effect size in terms of reduced relapse rate of currently authorised products is rather modest and any loss of efficacy will approach placebo.

Add-on designs as an alternative study design may be considered as long as an additive immunosuppressant effect is considered unlikely. In add-on trials one might include a third arm with the new product in monotherapy to establish if the superiority of the combination arm is due only to the new product or to the combination. A useful design is a 3-arm trial seeking superiority of the combination versus both products in monotherapy.

For compounds with an anticipated profound effect on the immune system and hence potential serious safety risks, a two step approach is recommended. As a first step, the product should be evaluated in a comparative superiority study versus first line therapy in patients apparently unresponsive to first line treatment and/or an (anticipated) rapid progression of their disease. In most cases it will not be possible to define whether remaining MS activity in this population reflects a lack of response to the current therapy or suboptimal response due to reasons such as increased disease activity. As a second step, provided the safety profile did not raise any concerns, superiority studies versus first line treatment /placebo may be considered to evaluate efficacy in the general multiple sclerosis population (see section 4.2.1).

As several subjective decisions and assessments will have to be performed, with a considerable risk of bias, all possible efforts should be done to keep the design double blind. In cases where double blind is not possible a blind observer design with a blinded examining physician different than the treating physician may be used. All measures to ensure reliable single blind evaluation should be guaranteed (i.e. patches that cover injection sites to hide reddening or swellings, education of examining physicians,…). Criteria to refer the patient to evaluation of a relapse should be established a priori in the protocol to avoid selective referral.

In SPMS patients, a claim of an effect on disability should be demonstrated in patients without superimposed relapses in case the product has activity against relapses.

In order to address the maintenance of the effect and to gather information on the long-term course of patients under treatment, an extended open label follow-up should be performed.

9. Safety

In addition to the general requirements, special efforts should be made to assess potential adverse effects that are characteristic of the class of drugs being investigated, for instance, occurrence of depression and seizures with interferons. A major category of products used or tested in multiple sclerosis are considered to act as immunomodulators. Therefore special attention should be given to the occurrence of serious infections and autoimmune diseases. Combining therapies with immune modulatory/suppressive effects may increase these risks.

9.1. Organ specific adverse events

9.1.1. Neurological adverse events

Special attention should be given to the occurrence of neurological adverse events or exacerbations of neurological symptoms as well as to the possible appearance of diseases related to suppression of immune responses within the CNS.

Also the effect of withdrawal of the test drug should be systematically monitored. At the time for application for a marketing authorization, it is expected that comprehensive data on clinical and/or MRI rebound after discontinuation is available. For MRI rebound, both number and volume of lesions must be evaluated. Such data can originate from an earlier stage of development, e.g. from a phase II trial that engaged a sufficiently long follow-up after discontinuation of study drug.

9.1.2. Psychiatric adverse events

Specific attention should be paid to the occurrence of depression/suicide and other psychiatric symptoms.

9.1.3. Others

Depending on the product, cardiac, hepatic or other organ specific signs and symptoms should be carefully monitored.

9.1.4. Long term safety

For chronic treatment, it is expected that at the time of marketing authorization, safety data of at least 2 years are available for a meaningful number of patients. Post-marketing drug utilisation studies, safety registries may be needed depending on safety of the product.

Given the potentially long-term use of an established drug therapy in multiple sclerosis, data on a large and representative group of patients for a sufficient period of time should be provided. As a major category of products used or tested in multiple sclerosis are considered to act as immunomodulators, special attention should be paid to autoimmune disorders and the tumour facilitating/inducing potential of these products. Full assessment of this effect could be done post-marketing. A pregnancy register may be considered.

A subcategory of the products used or tested in multiple sclerosis is biological products that may trigger the development of antibodies against the administered products or even to related molecules. Therefore, whether antibodies are developed and the impact of this on the long term efficacy (i.e. neutralising antibodies) and safety of the product should be investigated.

References

Ahlgren C et al. 'A nationwide survey of the prevalence of multiple sclerosis in immigrant populations of Sweden'. Mult Scler. 2012 August; 18(8):1099-107.

Arnold DL et al. 'Magnetic resonance imaging as a surrogate for treatment effect on multiple sclerosis relapses'. Ann Neurol. 2009 March;65(3):237-8.

Bermel RA et al. 'Multiple sclerosis: advances in understanding pathogenesis and emergence of oral treatment options'. Lancet Neurol. 2011 January;10(1):4-5.

Burton JM et al. '4-aminopyridine toxicity with unintentional overdose in four patients with multiple sclerosis'. Neurology. 2008 November 25; 71(22):1833-4.

Chabas D. 'Younger children with MS have a distinct CSF inflammatory profile at disease onset'. Neurology. 2010 February 2; 74(5):399-405.

Chitnis T et al. 'Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis'. Mult Scler. 2012 January; 18(1):116-27.

Cladribine: Withdrawal assessment report Movectro (Cladribine), Doc.ref: EMA/CHMP/351065/2010

Cohen JA et al. 'Disability outcome measures in multiple sclerosis clinical trials: current status and future prospects'. Lancet Neurol. 2012 May; 11(5):467-76.

Créange A et al. 'Walking capacities in multiple sclerosis measured by global positioning system odometer'. Mult Scler. 2007 March; 13(2):220-3.

Daumer M et al. 'MRI as an outcome in multiple sclerosis clinical trials'. Neurology. 2009 February 24; 72(8):705-11.

Ebers GC ey al. 'Disability as an outcome in MS clinical trials'. Neurology. 2008 August 26; 71(9):624-31.

Fampridine: European Public Assessment Report Fampyra (fampridine), Doc.Ref: EMA/555661/2011

Fingolimod: European Public Assessment Report Gilenya (Fingolimod), Doc.Ref: EMA/108602/2011.

Foley JF et al. 'Redefining functionality and treatment efficacy in multiple sclerosis'. Neurology. 2009 June 9; 72(23 Suppl 5):S1-11.

Hauser SL. 'Multiple lessons for multiple sclerosis'. N Engl J Med. 2008 October 23; 359(17):1838-41.

Hoogervorst EL et al. 'The patient's perception of a (reliable) change in the Multiple Sclerosis Functional Composite'. Mult Scler. 2004 February; 10(1):55-60.

Kappos L et al. 'Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study'. Lancet. 2008 October 25; 372(9648):1463-72.

Kaufman M et al. 'The significant change for the Timed 25-foot Walk in the multiple sclerosis functional composite'. Mult Scler. 2000 August; 6(4):286-90.

Kinkel RP et al. 'Association Between Immediate Initiation of Intramuscular Interferon Beta-1a at the Time of a Clinically Isolated Syndrome and Long-term Outcomes: A 10-Year Follow-up of the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance'. Arch Neurol. Published online October 10, 2011.doi:10.1001/archneurol.2011.1426.

Koch M et al. 'The natural history of secondary progressive multiple sclerosis'. J Neurol Neurosurg Psychiatry. 2010 September; 81(9):1039-43.

Koch-Henriksen N.'No shortcuts to outcome in MS clinical trials?'. Neurology 2009 February 24;72(8):686-7.

Li DK et al. 'Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-beta1a in relapsing-remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis'. Ann Neurol. 1999 August; 46(2):197-206.

Li DK et al.'MRI T2 lesion burden in multiple sclerosis: a plateauing relationship with clinical disability'. Neurology. 2006 May 9; 66(9):1384-1389.

Lotze TE. UpToDate. August 2012: 'Pathogenesis, clinical features, and diagnosis of pediatric multiple sclerosis'

Lotze TE. UpToDate. August 2012: 'Treatment and prognosis of pediatric multiple sclerosis'

Lou KJ et al. 'Markers for interferon responsiveness in multiple sclerosis'. Nature: *www.nature.com/scibx/.../scibx.2010.482.html*Vergelijkbaar. 2010

Lublin FD et al. 'Multiple Sclerosis and Other Inflammatory Demyelinating Diseases of the Central Nervous System'. Chapter 58, 1584-1612. Neurology in clinical practice 5th edition by Walter G. Bradley et al.

Neuteboom RF et al. 'Multiple sclerosis in children'. Ned Tijdschr Geneeskd. 2007 June 30; 151(26):1464-8. Dutch.

Olek MJ. UpToDate. August 2012: 'Clinically isolated syndromes suggestive of multiple sclerosis'

Olek MJ. UpToDate. August 2012: 'Comorbid problems associated with multiple sclerosis in adults'

Olek MJ. UpToDate. August 2012: 'Diagnosis of multiple sclerosis in adults'

583 Olek MJ. UpToDate. August 2012: ‘Epidemiology and clinical features of multiple sclerosis in adults’

584 Olek MJ. UpToDate. August 2012: ‘Multiple sclerosis Treatment of acute exacerbations of multiple
585 sclerosis in adults’

586 Olek MJ. UpToDate. August 2012: ‘Natalizumab for relapsing-remitting multiple sclerosis in adults’

587 Olek MJ. UpToDate. August 2012: ‘Treatment of progressive multiple sclerosis in adults’

588 Olek MJ. UpToDate. August 2012: ‘Treatment of relapsing-remitting multiple sclerosis in adults’

589 Perry J et al. ‘Classification of walking handicap in the stroke population’. Stroke. 1995 June;
590 26(6):982-9.

591 Polman CH et al. ‘Recommendations for clinical use of data on neutralising antibodies to interferon-
592 beta therapy in multiple sclerosis’. Lancet Neurol. 2010 July; 9(7):740-50.

593 Polman Ch. ‘Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria’. Ann
594 Neurol 2011; 69:292–302.

595 Ramagopalan SV et al. ‘Multiple sclerosis: risk factors, prodromes, and potential causal pathways’.
596 Lancet Neurol. 2010 July; 9(7):727-39.

597 Rice GP et al. ‘Interferon in relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev’. 2001;
598 (4):CD002002.

599 Sayao AL et al. ‘Longitudinal follow-up of "benign" multiple sclerosis at 20 years’. Neurology. 2007
600 February 13; 68(7):496-500.

601 Scalfari A et al. ‘The natural history of multiple sclerosis: a geographically based study 10: relapses
602 and long-term disability’. Brain. 2010 July; 133(Pt 7):1914-29.

603 Shirani, A et al. ‘Association Between Use of Interferon Beta and Progression of Disability in Patients
604 With Relapsing-Remitting Multiple Sclerosis’. JAMA. 2012; 308(3):247-256.

605 Sormani MP et al. ‘The distribution of magnetic resonance imaging response to interferonbeta-1b in
606 multiple sclerosis’. Neurol. 2005 December; 252(12):1455-8.

607 Sormani MP et al. ‘Combined MRI lesions and relapses as a surrogate for disability in multiple
608 sclerosis’. Neurology. 2011 November 1; 77(18):1684-90.

609 Sormani MP et al. ‘Magnetic resonance imaging as a potential surrogate for relapses in multiple
610 sclerosis: a meta-analytic approach’. Ann Neurol. 2009 March; 65(3):268-75.

611 Sormani MP et al. ‘Statistical issues related to the use of MRI data in multiple sclerosis’.
612 J Neuroimaging. 2007 April; 17 Suppl 1:56S-59S.

613 Sormani MP et al. 'Surrogate endpoints for EDSS worsening in multiple sclerosis. A meta-analytic
614 approach'. Neurology. 2010 July 27; 75(4):302-9.

615 Tenser RB et al. 'MRI as an outcome in multiple sclerosis clinical trials'. Neurology 2009; 73;
616 1933-1934.

617 Thompson AJ et al. 'Pharmacological management of symptoms in multiple sclerosis: current
618 approaches and future directions'. Lancet Neurol. 2010 December; 9(12):1182-99.

619 Tremlett H et al. 'Disability progression in multiple sclerosis is slower than previously reported'.
620 Neurology. 2006 January 24; 66(2):172-177.

621 Trojano M et al. 'Improving combination trials for multiple sclerosis'. Lancet Neurol.
622 2010 July;9(7):646-7.

623 Vermersch P et al. 'Clinical outcomes of natalizumab associated progressive multifocal
624 leukoencephalopathy'. Neurology 2011; 76:1697–1704.

625 Vukusica et al. 'Natural history of multiple sclerosis: risk factors and prognostic indicators'. Curr Opin
626 Neurol.2007, 20:269–274.

627 Waldman A et al. 'Childhood multiple sclerosis: a review'. Ment Retard Dev Disabil Res Rev. 2006;
628 12(2):147-56.

629 Wiendl H et al. 'Multiple sclerosis therapeutics: unexpected outcomes clouding undisputed successes'.
630 Neurology. 2009 March 17; 72(11):1008-1015.