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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).

Keywords	*Multiple Sclerosis, Guidance, Neurological Disease*

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

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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 study design, study population, primary endpoints and duration of the trials. Emphasis has been put on treatments that modify the disease progression which in general require long term superiority trials versus placebo or active comparator with the assessment of relapse and disability progression as the most important endpoints. Non-inferiority studies are an option provided assay sensitivity can be addressed. The time to relapse is considered acceptable as a primary endpoint. The need for alternative scales that assess disability is acknowledged and their development may be encouraged. At the moment, the Expanded Disability Status Scale (EDSS) remains the only validated outcome measurement to determine disability.

The data generated should allow for a separate benefit risk assessment for different degrees of disease activity in multiple sclerosis.

Symptomatic treatment focussing on the improvement of stable residual impairment would require randomised placebo controlled trials with symptom rating scales appropriate in the condition studied.

No further specific recommendations can be made as the objectives of symptomatic treatment are too diverse. The development of patient reported outcome measures is considered needed.

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 of multiple sclerosis 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. Generally it is assumed that MS is mediated by some kind of autoimmune process that is triggered by an infection which, superimposed on a genetic predisposition.

Approximately 85 % of all MS patients present 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 suffer from a relapsing-remitting form eventually develop sustained disability with or without superimposed relapses; this form is called the secondary progressive multiple sclerosis (SPMS). The term "relapsing MS (RMS)" applies to those affected patients either with a RRMS or SPMS with superimposed relapses. Patients with relapsing MS, in spite of suffering from different MS forms, constitute a common target for current treatment options. There are no clear criteria that mark the transition from RRMs to SPMS. Around 15% of patients develop a sustained deterioration of their neurological function early; i.e. primary progressive MS (PPMS). Some patients who start with a progressive deterioration may experience series of unresolved relapses with time and this form is called progressive relapsing multiple sclerosis. In others the deterioration occurs in the absence of relapses. Besides these main types of disease, a benign variety of MS refers to a RR form with only few relapses and no significant disability after several years of evolution. Conversely, the term malignant MS applies to a very aggressive form leading to severe disability or death in a few years after the onset of the disease.

The term clinically isolated syndrome (CIS) refers to the first clinical event that can be attributed to a demyelinating event but does not comply with the diagnostic criteria for definite MS i.e. dissemination of demyelinating events in time and space either observed clinically or radiographically.[1]

Pathophysiological processes involve acute inflammatory focal lesions, gliosis, demyelination, impaired remyelination, axonal loss and neuronal loss occurring 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 considered 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, and cognition disturbances among others. In general these treatments are non-specific. More MS specific treatments are those that intend to interfere with the pathophysiology of multiple sclerosis e.g. facilitate remyelination or axonal conductivity.

The standard of care for acute relapses is methylprednisolone i.v. Methylprednisolone shortens the duration of a relapse but has no influence on its sequelae. Plasmapheresis may improve recovery from relapse in steroid-resistant cases, but this is rarely used.

To date, treatments have aimed to modify the course of the disease mainly by suppressing or modulating the immune responses involved in MS pathogenesis. Biologicals (therapeutic proteins, monoclonal antibodies) and small molecules have been approved for use in this therapeutic context. These therapies aim to prevent relapses and ultimately intend to decrease the rate of accumulation of disability. Due to the risks (identified or potential) of opportunistic infections, malignancies, and other systemic adverse drug reactions, several of these treatment options are considered as second-line options i.e. treatment is restricted to patients with rapidly evolving multiple sclerosis or those who had a suboptimal response to prior therapies.

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 and symptomatic improvement. 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).

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

- 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).

- 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).

- Guideline on similar biological medicinal products containing monoclonal antibodies EMA/ CHMP/BMWP/403543/2010).

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 course of the disease. This includes:

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

 C) Treatment intended to improve an apparently stable residual disability.

4.1. Treatments of acute relapses

Neurological impairment due to a relapse may improve either completely or partially within weeks or few months. Regarding a specific relapse, the prediction of the course and degree of functional outcome is not possible. Therefore, randomised, double-blind, parallel group controlled clinical trials are needed to assess the benefit of any new therapy aimed to treat acute relapses. Possible endpoints are the duration of relapse and the degree of recovery from relapse at 3 and 6 months.

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 primarily descriptive, some differences in histopathology, also reflected in magnetic resonance imaging (MRI) activity exist.

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 a clinically isolated demyelination event and evidence of dissemination of lesions in time and space on the MRI.

Prevention and/or modification of relapse features as well as prevention or delay of the accumulation of disability due to relapses are meaningful goals of treatment in relapsing multiple sclerosis. Some of the currently approved therapies have demonstrated a favourable effect on the rate and severity of relapses as well as adelay in progression of disability in short-term studies (a few-years-duration). In reference to the current scientific view, an effect on relapses poorly correlates to prevention of disability. Therefore an effect on disability can not be claimed solely based on relapse prevention. For a distinct claim on disability large-scale long-term parallel group trials will be required to establish clinically relevant treatment effects on disease progression. Study duration will depend on the population studied, and should be sufficient to show a reliable and relevant effect on disability. Such a study may need to last ~3-years.

The improved diagnostic criteria for multiple sclerosis have led to the consequence that patients nowadays are diagnosed earlier and can participate in clinical studies at a much earlier stage of their disease. As a consequence the patients included in the current studies do have a significantly lower number of relapses as compared to the populations recruited in MS studies performed over the last decades. Thus the previously accepted position on what was considered a clinically meaningful effect on relapse rate may not be applicable anymore. Therefore companies should justify the clinical significance of any observed effect on relapse rate alongside its statistical significance.

For new drugs intended for the treatment of RMS, efficacy should be established by means of randomised double-blind (double dummy if needed) controlled parallel group trials. The preferred approach would be a development showing superiority versus placebo or an active comparator (i.e. first line DMTs like β -interferons, glatiramer acetate). A non-inferiority (NI) approach would also be acceptable, as long as assay sensitivity and a reasonable non-inferiority margin can be determined and properly justified, e.g. in cases when the an active comparator with consistent pronounced efficacy versus placebo or first/line DMTs. However non-inferiority trials versus first line DMT products like interferons or glatiramer acetate (or other products with a similar efficacy range), in the absence of a placebo arm, would not be sufficient, as in such a scenario an apparent efficacy could be explained by the regression to the mean, a 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.

In the development of new compounds intended to modify the natural course of multiple sclerosis, the anticipated benefit-risk profile of the product needs to be taken into account. This means that the expected benefit of treatment in consideration of disease activity and life expectancy of patients with multiple sclerosis, should be weighed against the anticipated risk for opportunistic infections, malignancies and other potential serious safety issues. 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 already approved indications or a known mechanism of action.

If a development aims at RMS as the intended indication, it should provide for separate conclusions at the time of the B/R assessment on the efficacy and safety in patients both with low and highly active

multiple sclerosis. The recommended approach will be that data on efficacy and safety are generated for both populations. In any case it has to be made possible to conclude that any efficacy as observed in the patients with low disease activity also translates into efficacy in the population with more active disease (see also section 8).

Add-on study designs may be considered as an alternative as long as there are no synergistic drug effects leading to increased safety concerns, e.g. a synergistic immunosuppressive effect. A useful design to be applied is a 3-arm trial looking at superiority of the combination versus both products used as monotherapy.

4.2.1.1. Clinically Isolated Syndrome (CIS)

Historically, patients with CIS were included in the indication of certain marketed products. For those products that do have CIS in the indication this has been restricted to patients with a clinically isolated syndrome at risk for definite multiple sclerosis based on the MRI picture. Nowadays, these patients would be diagnosed as having RRMS according to the revised diagnostic criteria for MS (Mc Donald's criteria 2010). Thus the inclusion of these patients in the study population for the development of new first line products for an indication in RRMS is acceptable.

The usefulness of developing products for patients with a "real" CIS that will not be classified as MS or inclusion of RIS (radiological isolated syndrome) is considered doubtful. If intended, a discussion at the level of Scientific Advice is recommended.

4.2.2. Secondary progressive multiple sclerosis (SPMS)

Patients with SPMS suffer from progression of disability with or without superimposed relapses. Prevention or delaying the accumulation of disability should be the goal of the treatment. As progression to disability often may take years, large-scale long-term, placebo-controlled, parallel group trials may be required.

To evaluate the efficacy of a product against disability progression in SPMS, it is recommended to target only SPMS patients without a recent relapse and no MRI activity suggestive of active inflammation, and with evidence of recent progression independently of relapses. This is needed to exclude possible effects of relapse activity on disability. However, occurrence of relapse activity needs to be assessed during the study and taken into account when determining confirmed progression of disability.

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. Randomised double-blind placebo-controlled clinical trials will be necessary in order to assess the efficacy on disability progression of any new treatment in primary progressive multiple sclerosis.

4.3. Treatments intended to improve apparently stable residual impairment

A number of symptoms (like cognitive deficits, impairments in motion and mobility, visual acuity, pain, bladder disturbances etc.) in an apparently "stable" disease from disease progression perspective, can have a serious effect on the MS patient's quality of life. Products developed in that context may

facilitate remyelination and repair, or be symptomatic in a stricter sense e.g. improve nerve conduction or cognition based on their mechanism of action.

Among the above symptoms, cognitive deficits are often reported as having the greatest impact on the patient's life. Thus, targeting improvement in cognition, but also in motion and mobility, visual acuity, pain or other symptoms, represents a valid treatment goal for new drug developments. If such specific symptomatic indications are strived for, separate randomised double-blind, placebo-controlled, parallel group trials will be needed. Endpoints in these trials may include validated scales measuring specific neurological symptoms, pain, cognitive functions, and other patient reported outcomes. However, although development is encouraged in that aspect, currently no specific recommendation can be made about the most appropriate tool for measurement of the effects on these symptoms in multiple sclerosis.

In the case of a development targeting an indication based on an effect on cognition, the main efficacy data should also be accompanied by data showing improvements in function or quality of life. As cognition is a broad concept, improvement on a single item performance test will be considered as insufficient. It should be clear that the cognitive impairment is specifically MS related. Hence the validity of the measurements of cognitive impairment in multiple sclerosis needs to be further justified.

What can be clearly stated, though, is that data on a functional outcome measure will be expected to be provided, in order to allow for the estimation of the clinical relevance of the symptomatic effect for the patient. Use of scientific advice or qualification procedures are recommended when such new approaches are considered.

4.4. Combination therapy

The development of combination therapies may be a beneficial approach.

When combining immunomodulators/-suppressants it should be clear that the same effect can not be obtained under monotherapy, i.e. the combination is aimed at   changing the benefit/risk balance in a favourable direction as compared to monotherapy.

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

A development testing the concomitant use of disease-modifying and symptomatic treatments is also a plausible approach. However, from a study design perspective it may interfere with the interpretation of the study results, as an observed effect might be attributable to both treatments whereas the contribution of the different treatments can not be disentangled. Therefore, the inclusion of monotherapy arms in addition to the combination arms may be helpful to address this. Alternatively a randomised placebo controlled study wherein symptomatic treatment is given on top of DMTs may be justified.

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 an additional

placebo arm for the internal validation of the study. Such study should include early escape conditions to allow for the use of 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 these so called "acute treatments" on the subsequent course of the disease (e.g. rate and severity of further relapses, progression of disability or even change from relapsing remitting into SPMS) is also considered relevant to assess.

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

5.2.1. Primary efficacy endpoints

A distinction should be made between accumulation of disability in relation to relapses in RMS 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 (See 6.1).

In patients with RRMS or SPMS with superimposed relapses (RMS), the primary efficacy parameter may be based on relapses, and both the annual relapse rate (ARR) and the time to relapse are considered acceptable as primary endpoints. A relapse-based primary endpoint though cannot be taken as a surrogate for disability progression and this would be expressed accordingly in the SmPC. Moreover, if the primary endpoint is based on relapse assessment, progression of disability should be evaluated as key secondary endpoint. From a safety perspective worsening of disability should be reasonably excluded by means of adequately powered long-term studies.

It would also be highly desirable to evaluate if the effect on progression is maintained on a long-term basis. As, in general, the course of multiple sclerosis with respect to disability is slow, this may need years of follow-up, e.g. 5 years or even longer. However, these data might be generated post-approval.

5.2.2. Secondary efficacy endpoints

- Disability. In studies where it is not the primary variable, it should be evaluated as key secondary endpoint
- Relapses (in studies where it is not the primary efficacy parameter). Recommended parameters are the time to relapse, annual relapse rate, frequency of moderate/severe relapses, proportion of patients free from relapses at a given time, proportion of subjects receiving rescue therapy.
- MRI derived parameters.
- Absence of disease activity, e.g. absence of MRI-activity, relapses and progression.
- Other measures related to disability e.g. neurological rating scales, measures of cognitive impairment, fatigue scales, ambulatory index.
- Clinical global impression of change as assessed by patient and physician.
- Patient reported outcomes (See 6.3).

6. Methods to assess efficacy

6.1. Progression of disability

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

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 EDSS score from the baseline is not an appropriate efficacy parameter. Instead progression should be predefined, e.g. as the achievement of a specified degree of disability or of a sustained worsening of a relevant magnitude (e.g. 1 point worsening when EDSS scores ≤ 5.5; 0.5 points if baseline score is > 5.5). Acceptable efficacy endpoints are the time to reach progression or the proportion of individuals who have shown progression at a pre-specified time.

An accurate and reliable definition of confirmed progression is important and should include two consecutive examinations carried out by the same physician at least 6 months apart. It is of paramount importance to obtain these two measurements in most of the patients for a reliable assessment of the results. It should be clearly specified in the statistical analysis plan how missing data and premature withdrawals are dealt with. Sensitivity analyses will need to be performed to evaluate the impact of different assumptions regarding missing data and, in particular, potentially informative censoring.

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 neurological performance tests (e.g. MSFC) may be used as secondary measurements of disability.

The advantages and disadvantages of the EDSS in assessing disability in MS are well-known. Therefore, there is a recognised need for the development of alternative sensitive scales that assess disability. However, at the moment, no specific recommendations regarding the acceptability of alternative scales can be given as several scales are still under development and need first to be validated. If in the future they are accepted, it is advised to still use the EDSS as an additional secondary endpoint in clinical trials in order to facilitate cross comparisons with other studies.

6.2. Relapses

Time to relapse and the annualised relapse rate are acceptable parameters to assess relapse-status. The *a priori* definition of responders in terms of absence of relapses is recommended.

Identification of a relapse might be difficult as patients frequently suffer from pseudo-exacerbations caused by infection, heat or stress. An accurate definition of relapse (its 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, etc.) 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.

Time to relapse would limit the exposure to placebo or the time during which the patient experiences suboptimal active control of his symptoms. However, even if an effect on time to relapse is shown,

maintenance of the effect on relapses should be demonstrated. Thus, time to relapse is acceptable as a primary endpoint provided that data are generated to show maintenance of effect. Time to second or third relapse may be useful for this.

For relapse rate the analysis model should be specified in the study protocol and ensure type-I 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. Symptomatic treatment

Symptomatic treatment may focus on improvement of stable residual impairment e.g. impairments in motion and mobility, visual acuity, pain, fatigue, bladder disturbances, cognitive deficits among others.

No specific recommendation can be made regarding the appropriateness of assessment scales as the objectives of symptomatic treatment are too diverse. In general the scales will use should have been validated and sensitive to change. Moreover the use of clinical global impression of change scales both, by patient and by the physician may be helpful to link the observed changes on the specific rating scales to a perceived clinically relevant effect. Use of scientific advice or qualification procedures are recommended when uncertainty exist on the best approach.

6.4. Health related Quality of Life (HR-QoL)

Few data are available on validation of specific instruments for QoL in patients suffering from 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.

The development of patient reported outcomes is encouraged. Several patient reported outcomes are under evaluation. Their use and validity in multiple sclerosis should be justified in the study protocols. So far limited data are available. Hence specific recommendations on specific scales can not be made.

6.5. 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. New MRI-based variables for disease monitoring are under evaluation (brain atrophy, visualizing myelin) and may be considered helpful for assessing outcomes in future drug development, provided sufficient data on their validity and relevance are available.

The possible correlation between MRI parameters and long-term clinical outcome 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 potentially be useful.

So far, MRI measurements have not been demonstrated to be a reasonably validated surrogate endpoint for the clinical outcome and are, therefore, not acceptable as a primary endpoint in pivotal studies evaluating new agents. MRI findings are useful as a first indication of dealing with a potentially

clinically effective product, e.g. in proof of concept studies and dose-finding studies. In pivotal studies MRI is an useful tool to evaluate the consistency with the clinical effect.

However, MRI criteria used so far predominantly focus on the inflammatory component. Potential useful treatments may be missed by screening agents in MS on MRI criteria only. This may be especially true 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 as well as adequate training should be followed.

Reading of MRI images should be central and blinded.

As discussed in the relevant guideline (see section 3), for demonstrating clinical similarity of a biosimilar and reference product, magnetic resonance imaging of disease lesions in RMS may be sufficient. In addition, clinical outcomes such as relapse rate or percentage of relapse-free patients should be used as secondary endpoints in support of the MRI outcomes. These principles are also valid in the context of a generic application.

7. Selection of patients

7.1. Diagnostic criteria

The revised McDonald's criteria (2010) incorporating MRI criteria for dissemination in time and space, are widely accepted.

7.2. Type of patients

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

As stated in section 4.2.1 sufficient data need to be generated that allow a separate assessment of the benefit risk in the mild and highly active multiple sclerosis population.

Although there is no consensus regarding the exact criteria for mild and highly active multiple sclerosis, the distinction is based on a combination of persisting clinical relapses despite treatment and disease activity according to MRI-derived criteria. Hence, the precise definition of highly active disease should be stated and justified in the study protocol. 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. Stratification for milder and more severely affected patients is recommended.

In trials intended to evaluate the relapse rate, it is recommended not to include SPMS subjects with superimposed relapses as this might complicate trial design and hamper the interpretation of the effect on relapses and disability. It is reasonable to assume that relapses in RRMS and SPMS have the same underlying inflammatory pathophysiology and therefore efficacy on relapses in RRMS patients may be extrapolated to efficacy on relapses in SPMS. However, extrapolation of the effect on disability will not be considered appropriate as pathophysiology is different.

For treatments aimed to improve a stable neurological impairment, facilitate remyelination or improve axonal conductivity, the patient population may be broader as long as it can reasonably be excluded that the course of multiple sclerosis does not interfere with the assessment of efficacy of these treatments. Stratification of patients for the different subpopulations (e.g. SPMS, RRMS), will allow evaluation of efficacy in these subgroups.

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

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 resemble that of adult-onset RRMS. However, compared to adult onset RRMS, especially younger children appear to have more frequent relapses, earlier cognitive deficits, recover 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, generation of specific data is expected. Depending on the mechanism of action, the expected safety profile and the targeted age group this could be done by performing clinical trials tailored to children, by incorporating adolescent MS patients into the adult trials, and/or by partial extrapolation of efficacy from adult trial(s). The approach chosen should be justified and depends among others on the mechanism of action, on the availability of suitable biomarkers for efficacy as confirmed by the adult trials and on the existence of a valid pharmacokinetic target exposure.

Trials in children should only be initiated when there is sufficient evidence that the product may meet a paediatric medical need with a suitable safety profile.

Data on safety in children should be generated. Considering the life-long treatment, this should include long-term safety data concerning immune response to infectious disease – vaccination when appropriate, mental, cognitive function, growth and sexual development. All patients should preferably be included in registries to monitor long-term safety and efficacy.

Elderly patient population
Newly diagnosed multiple sclerosis in the elderly is rare. However elderly patients with multiple sclerosis will be treated for their multiple sclerosis already diagnosed at an earlier age. Hence the safety data base should be sufficient to allow an assessment of the safety in the elderly.

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 and other non-clinical model where available (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 hypotheses 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. Human studies of pharmacodynamic interaction between putative combinations are necessary prior to conducting 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 the goal of treatment. However, to maximise possible treatment contrast, it seems reasonable to choose patients with predictors of high clinical activity and with only moderate disability.

In exploratory trials in RMS, the use of MRI derived parameters as the main endpoint for assessing preliminary efficacy or dose-finding is acceptable where applicable (see 6.2). Relapses and other clinically meaningful outcomes should also be evaluated.

Depending on the proposed mechanism of action and stage of the disease 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 deterioration in neurological function should also 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 of a large scale and of sufficient duration to allow for the evaluation of an effect on relapses and disability. The duration of a study intended to demonstrate a clinically meaningful effect on relapses will depend on the activity of the population studied and in cases of a prevalent population with a milder disease course may need to last 3-years.

For the development of new drugs in the treatment of MS the preferred approach would be that efficacy be established by means of randomised double blind (double dummy if needed) controlled

superiority trials. Superiority might be shown against placebo or first line treatment, as discussed in section 4.2.1. A non-inferiority design versus first line treatments like interferons or glatiramer acetate (or other products with similar efficacy) will create difficulties as their effect size in terms of reduced relapse rate is rather modest and any loss of efficacy will be close to the effect seen in placebo patients. Nevertheless non-inferiority studies remain an option, provided assay sensitivity is properly addressed (see section 4.2.).

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 monotherapy arm with the new product 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.

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 a double blind evaluation 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 follow-up either blinded or open label 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 , autoimmune diseases and events related to a decreased immunosurveillance. 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 activity after discontinuation are available. 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, risks of infection, immune related safety, 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. The risk of opportunistic infections, malignancies may be needed to address 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 related molecules. Therefore, whether antibodies developed has to be evaluated as well as the impact of this on the long term efficacy and safety.

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