



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE
TREATMENT OF MULTIPLE SCLEROSIS**

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EXECUTIVE SUMMARY

This Guideline is intended to provide guidance for the evaluation of drugs for the treatment of multiple sclerosis. It should be read in conjunction with the Directive 75/318/EEC, as amended, and other current and future CHMP and ICH guidelines, in particular the guidelines on:

- Statistical principles for clinical trials (ICH topic E9)
- The extent of population exposure to assess clinical safety (ICH topic E1)
- Pharmacokinetic studies in man
- Dose response information to support drug registration (ICH topic E4)
- Investigation of drug interactions
- Choice of control group in clinical trials (ICH topic E 10)

1. INTRODUCTION (background)

Multiple Sclerosis (MS) is a common neurological disease affecting more than 1 million people worldwide. Its prevalence rate varies between races and geographical latitude, ranging from more than 100 per 100,000 in Northern and Central Europe to 50 per 100,000 in Southern Europe.

MS is an inflammatory condition that damages the myelin of the Central Nervous System and causes neurologic impairment and, frequently, severe disability. It is the commonest cause of neurological disability in young and middle-aged adults and has a major physical, psychological, social and financial impact on patients and their families, friends and bodies responsible for health care.

The aetiology of MS remains unknown. It is generally assumed that MS is mediated by some kind of autoimmune process possibly triggered by infection and superimposed upon a genetic predisposition. As many as 80 to 85 % of all patients present with a form of disease known as relapsing-remitting MS (RRMS), which is characterised by unpredictable acute episodes of neurological dysfunction named clinical attacks or 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; this form is called 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 (PRMS). Besides these main types of disease, the benign variety of MS refers to a RRMS 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.

Finally, the term clinically isolated syndrome (CIS) applies to those patients who have suffered a single clinical event but do not comply with the diagnostic criteria for definite MS.

It is unclear whether the different courses of MS described are due to the same or to distinct pathophysiologic processes. Relapses are considered the clinical expression of acute inflammatory focal lesions whereas progression is considered to reflect the occurrence of demyelination, axonal loss and gliosis. Relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis are probably different stages of the same disease while primary progressive multiple sclerosis may imply different processes.

In general, current therapeutic approaches include:

Symptomatic treatment. This refers to all therapies applied to improve symptoms caused by the disease: fatigue, spasticity, ataxia, weakness, bladder and bowel disturbances, sexual dysfunction, pain, tremor, paroxysmal manifestations, visual impairment, psychological problems, cognitive dysfunction and other associated conditions that can improve with non specific treatments. Clinical development of these products is out of the scope of this guidance.

Treatment of acute relapses with corticosteroids

Treatment aimed to modify the course of the disease. In this category there are therapies aimed to decrease the relapse rate or modify relapses; therapies aimed to diminish the accumulation of disability in time; and future therapies that pursue neuroprotection or intend to restore neurological function (e.g. by means of promotion of remyelination).

Recent studies suggested that progression of lesions in MS might have, even in early clinical stages, two components: an active immunological aspect and a degenerative aspect; it is unknown to what extent these are causally interrelated. Currently approved therapies to modify the MS course target the immunological processes of the disease. Most of them are considered to act as immunomodulators but their mechanisms of action have not been completely elucidated: the relationships between changes of the immune response induced by these agents and the clinical efficacy in MS is far from settled. Immunosuppressants or cytotoxic agents are also used in some patients after failure of conventional therapies.

Based on the immunological nature of the disease, combination therapy targeting different parts of the immune processes may be reasonable and development of a new treatment as a combination therapy is a possible strategy.

2. SPECIFIC CONSIDERATIONS WHEN DEVELOPING PRODUCTS FOR THE TREATMENT OF MULTIPLE SCLEROSIS

2.1 Different goals of treatments

Treatments of MS may have different goals that will lead to 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. This may refer to the sustained accumulation of disability related with relapses or to the progression of disability either in the progressive phase of the disease (SPMS) or in PPMS. Those three situations demand a separate approach.
- Preventing or modifying relapses. It is not clear to what extent the effect on relapses is related to the prevention or delay in the long-term accumulation of disability, which is considered a more clinically relevant effect

C) Improvement of an apparently stable residual disability

2.2 Treatments for acute relapses

Neurological impairment due to a relapse may improve spontaneously within weeks or few months. However, regarding a specific attack, prediction of the course and degree of later functional recovery is not possible. Therefore, parallel controlled clinical trials are mandatory to assess the benefit of any new therapy.

Corticosteroids are the accepted treatment for acute relapses in MS. Plasmapheresis is used in severe relapses based on limited data. Corticosteroid therapy shortens the duration of the relapse and accelerates recovery, but there is no evidence that corticosteroid treatment improves the overall degree of recovery or alters the long-term course of the disease. These are relevant issues when investigating new treatments for relapses.

As there is no agreement about the specific criteria of corticosteroid treatment (e.g. dosage, method of administration, tapering,..) the actually chosen regimen should be stated and justified in the protocol.

If, for a test drug only an effect on the duration, severity and/or recovery from a relapse is claimed, this claim should be based on clinical trials with corticosteroid treatment as positive control and a placebo arm for the internal validation of the study. Even if only relapses with homogeneous signs or symptoms are considered, it is recognised that it is difficult to give a reliable assessment of the

severity of a relapse, either using clinical judgement or neurological scales. MRI with gadolinium may inform on the duration of the inflammatory activity.

The trial should include escape conditions to allow switching to standard therapy when the patient fails to improve or even 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. It is recommended also to investigate the modification of the subsequent clinical course of the disease in terms of time free from subsequent relapse and progression of disability. The investigation of a modifying the effect on other products being used concomitantly as chronic treatments intended to modify the natural course of the disease, may be also valuable.

If an effect is claimed with regard to the degree of recovery after a relapse and/or the long-term course of the disease, this should be demonstrated by means of placebo-controlled superiority trials.

2.3 Treatments intended to modify the natural course of the disease

It is important to differentiate between the clinical patterns of the disease: RRMS, SPMS with and without relapsing activity and PPMS (see 1.). Although these patterns are defined according to clinical features (occurrence of relapses, presence of gradual progression of disability) differences in histopathology and MRI (Magnetic Resonance Imaging) activity are also present.

2.3.1 Relapsing multiple sclerosis

The term relapsing MS includes 1) patients with RRMS, 2) patients with SPMS and superimposed relapses and 3) patients with a single demyelinating clinical event who show lesion dissemination on subsequent MRI scans according to McDonald's criteria.

Prevention and/or modification of relapse features as well as prevention or delay of the accumulation of disability as sequelae of acute relapses, are meaningful goals in the treatment of RMS

Progression of disability, as a result of relapses from which patients do not fully recover take many years and, for the moment, there are no surrogate variables for evaluating progression of disability. Therefore large-scale long-term parallel group trials are required to establish clinically relevant treatment differences on disease progression.

Relapse rate, relapse duration, recovery after relapses are all highly variable between patients and within one patient. Therefore, treatments intended to decrease the relapse rate or modify relapses should be evaluated in parallel trials sufficiently large and long to overcome this inter and intra-individual variability.

Currently approved therapies have demonstrated a favourable effect on the rate and severity of relapses and some products also in the short-term (a few years) progression of disability. If a product demonstrates a benefit in relapse rate or severity without an accompanying effect on preventing or delaying disability, the clinical relevance of such benefit should be justified. For this reason studies aimed to evaluate an effect on relapse rate should also generate data with respect to disability.

Although the effect on relapse rate may be investigated in patients with any form of relapsing MS, it is advisable to assess the effect on disability only in patients with relapsing remitting MS. It is therefore accepted that the indication in relapsing MS will mainly rely on the effects shown in patients with relapsing remitting MS and that an effect on relapses in relapsing remitting MS may be extrapolated to an effect on relapses in secondary progressive MS.

Several major placebo-controlled clinical trials have provided evidence of an apparent short-term stabilisation in placebo-treated patients that could be explained, among others, by the regression to the mean phenomenon, and by a real placebo effect, as well as by the natural course of the disease. Approved therapies have been shown to favourably modify the short-term evolution of the disease although the benefit is modest, at the cost of significant inconveniences and side effects and it is not known whether the effect is maintained for years. Differences from placebo are not consistent across trials and the sensitivity of the available scales to measure progression of disability as well as other characteristics of clinical trials in this field do not assure the ability to detect clinically relevant differences.

Therefore, equivalence (non-inferiority) trials are insufficient, as the only proof of efficacy and demonstration of superiority against placebo or active comparator should be provided.

Since it is anticipated that placebo-controlled clinical trials may raise problems of feasibility and even some ethical concerns, different approaches and alternative designs may be explored in order to circumvent these constraints. Although a three-arm trial including a placebo and an active control is a preferred design, it is recognised that it would be very difficult to undertake unless modifications to the design were introduced (e.g. a short duration three-arm trial, one-year placebo or placebo until patients have a new relapse, after which these patients will be drop out and subsequent parallel trial with only the two active arms). The proportion of subjects with no relapses over two years of follow-up then may be the primary endpoint. Other options may include add-on designs, placebo-controlled clinical trials in selected populations such as those refusing treatment after being well informed of available therapies or those where the benefits of current therapies are less clear.

2.3.1.1 Clinically Isolated Syndrome (CIS)

Patients with CIS are not considered an appropriate target for pivotal clinical trials aimed to demonstrate efficacy of products in MS.

When a population in early stages of the disease and at high risk for further relapses is selected, it is expected that effects of treatments preventing further relapses may be of a greater magnitude. At the same time, however, the clinical relevance of the effect (with respect to long-term benefit) is less clear.

Therefore it is difficult to extrapolate positive results in CIS patients to relapsing remitting MS. However, they may constitute either supportive evidence of efficacy in MS or an additional claim for a product with a demonstrated efficacy in relapsing remitting MS.

In CIS, the delay of the occurrence of a second clinical attack, although relevant from a mechanistic perspective, is of limited clinical relevance. It is needed to demonstrate efficacy by means of a meaningful and sustained decrease in relapse rate over 2-3 year time and it is recommended to assess the decrease of the accumulation of disability.

2.3.2 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.

In trials conducted in patients with SPMS it is important to differentiate those patients with relapses from those without relapses, as some medications might favourably alter disability due to sequelae from acute attacks with no detectable effect on pure progression and, therefore, generalisation of the effect to patients without relapses would not be possible.

2.3.2.1 SPMS with superimposed relapses

Treatments focused on modifying relapses may be useful in patients still suffering relapses. This situation is covered under the indication of treatment for relapsing MS. However, it must be taken into account that some effect on relapses without an accompanying effect on disability may be considered, in these patients, less important than in RRMS. Therefore, the benefit-risk assessment of a new therapy might need to be done separately for those patients.

2.3.2.2 SPMS without superimposed relapses

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.

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

2.3.3 Primary progressive multiple sclerosis (PPMS)

So far, clinical trials have not shown efficacy in this type of patients. Randomised, double-blind placebo-controlled clinical trials are necessary in order to assess the efficacy of any new treatment in PPMS.

2.4 Treatments intended to improve apparently stable residual impairment

Improvement of a fixed neurological impairment is a worthwhile treatment goal on its own in MS. Some products that potentially facilitate remyelination or improve nerve conduction are being developed. As the clinical experience with this new type of products is very limited, specific recommendations cannot be made.

2.5. Combination therapy

The limited efficacy observed with the authorised medicines and the possible intervention in several steps of the immune response or even in other pathological features of the disease (e.g. neuroprotection,...) suggests the possibility of combination therapies as a suitable approach.

When combining therapies, in addition to general safety concerns, several aspects should be considered. First, it is possible that combination of useful immunomodulators does not improve efficacy or even may show less efficacy due to some antagonisms in their complex respective actions. Second, the possible risk of a too potent suppression of the immune response should be considered with respect to, e.g. infectious processes at the Central Nervous System and inhibition of existing remyelination.

3. CRITERIA FOR ASSESSMENT OF EFFICACY IN CONFIRMATORY TRIALS

3.1 Treatment of acute relapses

Duration and severity of relapses and overall recovery or prevention of sequelae are relevant parameters. The duration of the gadolinium enhancement of T1 lesions is indicative of inflammatory activity and may be included as a secondary variable.

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. Therefore, long-term trials are also recommended to evaluate the benefit-risk ratio of a new treatment for acute relapses.

3.2 Treatments aiming to modify the natural history of the disease

3.2.1 Primary efficacy parameters

The most relevant parameter in MS is the accumulation of disability usually takes place over many years. Changes in progression of disability in a few years, which can be shown in clinical trials, could be accepted as a proof of efficacy, although it would be highly desirable to evaluate if the effect is maintained on a long-term basis.

It should be distinguished 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 also be the relapse rate although the number, duration or severity of relapses cannot be taken as a surrogate for disease progression and this would be expressed accordingly in the SPC. Moreover, progression of disability should be evaluated and worsening of disability should be reasonably excluded by means of adequately powered long-term studies.

In patients with CIS the relapse rate and the percentage of patients with no further relapses are preferred efficacy variables instead of the time to the second clinical event. As in other MS forms, accumulation of disability is considered a relevant efficacy parameter that should be evaluated.

3.2.2 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.

- MRI derived parameters.
- 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,...).

4. METHODS TO ASSESS EFFICACY

4.1 Progression of disability

Progression of disability should be assessed by means of valid, sensitive and reliable scales. Intra- and inter-observer reliability should be known or assessed.

The Kurtzke'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 neuro-performance tests (e.g. MSFC) or patient and neurologist global opinion may be used as secondary measurements of disability.

4.2 Relapses

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.

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) may be difficult to interpret in terms of clinical relevance and it is not considered a good primary endpoint in confirmatory trials

The annualised relapse rate is an acceptable parameter to assess relapses. The definition a priori of responders in terms of relapses (e.g. patients with ≤ 1 relapse) may be a useful variable.

4.3 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. For example, the appearance of 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, the correlation between Magnetic Resonance Imaging and clinical outcomes has not proved to be strong enough as to accept it as a validated surrogate 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.

New MRI techniques such as spectroscopy, magnetisation transfer or diffusion tensor have been developed. These neuroimaging procedures, as well as other new techniques, could be studied in future trials in order to increase the knowledge and try to validate them as a possible surrogate parameters for clinical outcome.

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.

4.4 Health-related Quality of life (HRQoL)

Few data are available on validation of specific instruments for HRQoL in patients suffering MS. If a claim with respect to HRQoL in MS is considered, reliable and validated scales should be used.

5. SELECTION OF PATIENTS

5.1 Diagnostic criteria

Nowadays, the revised McDonald’s criteria (2005), which incorporate MRI are widely accepted.

It is also possible to use the classical Poser’s diagnostic criteria for MS, based on patient history, clinical examination, CSF studies, evoked potentials, and exclusion of alternative diseases.

5.2 Type of patients

Depending on the purpose of the trial, different subgroups of patients should be selected a priori. 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.

Extrapolation from one subgroup of patients to others may not be possible.

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. However, inclusion of therapy resistant patients should be avoided as they form a separate subgroup. Exclusively selection of therapy resistant patients is possible when the product is intended for this clinical setting, and a restricted indication will probably be obtained in this case. Appropriate definitions of non-response or suboptimal response should be verifiable and prospectively defined.

In trials intended to evaluate 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.

5.3 Special populations

Currently available data of MS below the age of 16 years are limited. Therefore, a formal recommendation for this population can not be given. Generation of paediatric data is encouraged in order to support such recommendation.

6. STRATEGY-AND DESIGN OF CLINICAL TRIALS

6.1 Pharmacodynamics

The proposed mechanism of action should be described 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.

6.2 Pharmacokinetics

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

6.3 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.

6.4 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, is acceptable (see 4.3). Usually, studies will have a parallel double blind design and duration of 6 month may be adequate. Relapses and other clinically meaningful outcomes should also be evaluated.

In SPMS or PPMS, disability should be assessed in addition to supportive MRI and longer duration of the trial will be needed.

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.

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, remyelination and pharmacogenomics. It is therefore expected that this is made 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.

6.5 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.

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.

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 (some active comparator trials, some easily unblinded treatments,...) 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.

The use of two or more different dosage regimens is advisable if no conclusive results have been obtained from previous studies.

Efficacy demonstration should rely on a superiority trial either versus placebo and/or to any available single therapy either in terms of relapse reduction or prevention of accumulation of disability.

The known limitations of non-inferiority trials as a proof of efficacy are especially applicable to the demonstration of efficacy in MS. A non-inferiority design will raise difficulties as the effect size in terms of reduced relapse rate of currently authorised product is rather modest and any loss of efficacy will approach placebo. Under these circumstances, a reasonable non-inferiority margin will be so small that the trial in practice will be close to a conventional superiority trial. Therefore, as stated, non-inferiority trials are insufficient as the only proof of efficacy.

A non-controlled design and the use of a comparative cohort of placebo-treated patients from past trials as an historic control is not acceptable as a proof of efficacy (see 2.3.1).

Active control parallel group trials comparing the new treatment to an already approved treatment are needed in order to give the comparative benefit/risk ratio of the new treatment, at least in those treatments intended to prevent relapses. Three-arm studies with placebo, test product and active control are a preferred design although feasibility of long-term placebo controls has become seriously limited due to the evidence of efficacy of available treatments.

An option is to compare the new treatment to placebo in a short duration phase (e.g. one year or until patients have a new relapse) and thereafter to switch placebo-treated patients to a predefined active treatment or randomise them to the experimental product or a predefined active treatment. The proportion of subjects with no relapses over two years of follow-up then may be the primary endpoint. If the product is to be used in combination, a placebo-controlled trial of 2-3 year duration, as an add-on treatment is an acceptable design.

In most cases with individual patients on therapy, it is not possible to define whether remaining MS activity signifies lack of response to the current therapy or suboptimal response due to reasons such as increased disease activity. It is therefore recommended that “second line” trials should include a study arm with continued therapy with the apparently failing compound. In add-on trials it is recommended to include a third arm with the new product in monotherapy as it may be difficult 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.

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.

7. SAFETY

Identified adverse events should be characterised in relation to the duration of treatment, the dosage, the recovery time, age and other relevant variables. Clinical observations should be supplemented by appropriate laboratory tests and ECG recordings.

All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of serious adverse drug events, adverse events leading to dropouts and patients who died while on therapy.

Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self-poisoning should be provided.

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 MS 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.

7.1 Organ specific adverse events

7.1.1 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 authorisation, it is expected that comprehensive data on clinical and/or MRI rebound after discontinuation is available in a meaningful number of patients. 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.

7.1.2 Psychiatric adverse events

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

7.1.3 Others

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

7.2 Long-term safety

Given the potentially long-term use of an established drug therapy in MS, 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 MS 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.

At the time of marketing authorisation, it is expected that safety data of at least 2 years are available for a meaningful number of patients.

A subcategory of the products used or tested in MS are 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.