European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 15 September 2005
Doc. Ref. EMEA/CHMP/EWP/561/98 Rev 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

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

DRAFT AGREED BY EFFICACY WORKING PARTY	28 June 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	15 September 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2006

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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 (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 (SP). 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 (PP) MS. 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.

Finally, the term clinically isolated syndrome (CIS) applies to those patients who have suffered a first clinical attack but do not comply with the classical diagnostic criteria for definite MS. Nowadays, the presence of new lesions in a second MRI performed at least three months apart is an accepted criterion for a diagnosis of MS in these patients.

It is unclear whether the different courses of multiple sclerosis 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.

The current therapeutic approach is

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).

Currently approved therapies to modify the MS course target the inflammatory 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 multiple sclerosis is far from settled. Immunosupressants 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 multiple sclerosis may have different goals that will lead to different clinical development plans and clinical trial designs:

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

2.1.2 Modification of the natural history of the disease. This includes:

- Preventing or delaying the accumulation of disability
- Preventing or modifying relapses. It is not clear to what extent effects on relapses are related to the prevention or delay in the long term accumulation of disability, which is a more clinically relevant effect

2.1.3 Improvement of an apparently stable residual disability

It is uncertain to what extent the effect on relapses is related to prevention of disability. Therefore if claims related to improvement of residual disability are made for an agent with activity against relapses, an effect in disability should be proven separately in patients with non-relapsing MS.

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.

The trial should include early escape conditions to allow rescue treatment 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 to also 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 the possibility of modifying the effects of 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: relapsing remitting multiple sclerosis, secondary progressive multiple sclerosis with and without relapsing activity and primary progressive multiple sclerosis (see introduction). 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 clinically isolated syndromes (CIS) 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 relapsing multiple sclerosis.

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.

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

Several major placebo controlled clinical trials have provided evidence of an apparent short term stabilisation in placebo treated patients that could be explained 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 and subsequent parallel trial with only the two active arms). Other options include superiority trials against active control, 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

Patients with CIS complying with Mc Donald's criteria may be considered relapsing MS and therefore, covered by an approval for the treatment of RMS. Nevertheless, the demonstration of clinical benefit of a given treatment in this population has some peculiarities.

The delay of the occurrence of a second clinical relapse, although relevant from a mechanistic perspective, is of limited clinical relevance. It is needed to demonstrate efficacy by means of a decrease of the accumulation of disability, or at least a meaningful and sustained decrease in relapse rate over 2-3- year time. This is particularly important if the efficacy in these patients would be used as a main support for the approval of a new product, instead of being an additional claim for an already approved product.

Extrapolation of efficacy results from CIS to clinically definite RRMS may be difficult. 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. Clinical trials in these patients should be long enough to address both the absolute efficacy of the product and the benefit versus deferred start of conventional therapy for clinically definite MS.

Finally, patients with CIS but without diagnosis of MS according to McDonald criteria are not considered an appropriate target for clinical trials aimed to demonstrate efficacy of products in multiple sclerosis.

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 secondary progressive multiple sclerosis 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

The course of primary progressive multiple sclerosis is less variable as compared to relapsing remitting or secondary progressive multiple sclerosis. 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 primary progressive multiple sclerosis.

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 multiple sclerosis. 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 re-myelinisation.

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.

However, 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 secondary progressive multiple sclerosis) is also relevant. Therefore, also long-term trials are 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 primary efficacy parameter in confirmatory trials should be a clinically measured prevention or delay of the disability progression. Accumulation of disability in multiple sclerosis usually takes place over many years. However, 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.

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

3.2.2 Secondary efficacy end points

- Disability. In studies where it is not the primary variable, it is a very important secondary end point.
- 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, for instance total lesion load by using serial measurement of T2-weighted magnetic resonance images.
- 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-rater and interrater 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 multiple sclerosis.

The disadvantages and advantages of the EDSS in assessing disability in multiple sclerosis are well known. Therefore, on the one hand the development of alternative scales for assessing disability in multiple sclerosis 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-rater reliability, all possible actions intended to increase reliability of the scale should be adopted: training of raters, 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 $\leq$ 5.5; 0.5 points if baseline score is >5.5). Acceptable efficacy parameters end points are the time to reach progression or the proportion of individuals who have shown progression at a prespecified time.

Accurate and reliable definition of sustained worsening is important and should include two consecutive examinations carried out by the same physician at least six 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's and neurologist's 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.

Decisions on relapses should be taken 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 neither in RRMS nor in CIS patients and more robust proof of efficacy should be undertaken.

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 clinically isolated syndromes, relapsing remitting and secondary progressive multiple sclerosis with relapses.

In non relapsing secondary progressive multiple sclerosis and primary progressive multiple sclerosis, measures of CNS atrophy including grey and white matter volumes, and new MRI techniques (vide infra) may be useful.

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. Total lesion load (on T2 weighted images), chronic T1 weighted hypointensity (chronic "black holes") and several brain atrophy measures have been related to tissue loss and are increasingly used. So far, such correlation has been found to be weak and not of predictive value for clinical outcome. Therefore Magnetic Resonance Imaging is not a validated surrogate end point for clinical outcome in pivotal studies. In exploratory trials, however, changes in MRI findings in relapsing remitting multiple sclerosis or secondary progressive multiple sclerosis, may be used as a first indication of dealing with a potentially clinically effective product.

New MRI techniques such as spectroscopy, magnetization 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 Quality of life (QOL)

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

5. SELECTION OF PATIENTS

5.1 Diagnostic criteria

Nowadays, the McDonald's criteria, which incorporate MRI are widely accepted. In CIS they allow the demonstration of lesion dissemination in space and time using MRI data on repeat scans taken at least three months after the onset of the clinical event.

It is also possible to use the classical Poser`s diagnostic criteria for multiple sclerosis, 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.

Selection of patients with suboptimal response to previous standard therapies should be avoided in active comparative trials and naïve patients are preferable for such comparisons, unless the product is clearly intended for this clinical setting (e.g. products with preliminary proof of efficacy but existing safety issues). In this case, appropriate definitions of non response or suboptimal response should be verifiable and prospectively defined .

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 relapsing remitting or secondary progressive multiple sclerosis, the use of MRI derived parameters as the main end point is acceptable (see 4.3.MRI). Usually, studies will have a parallel double blind design and a duration of 6 month may be adequate. Progression of disability, 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.

The search for valid biomarkers of disease activity, therapeutic activity and long-term prognosis is pivotal. 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 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

Pivotal trials should have a double blind parallel design. The main efficacy end point depends on the goal of the treatment**.**

The annual relapse rate in relapsing remitting multiple sclerosis 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.

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.

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

Efficacy should be demonstrated by means of a superiority trial versus placebo or any available single therapy either in terms of relapse reduction or prevention of accumulation of disability.

A non controlled design and the use of a comparative cohort of placebo patients from past trials as an historic control is not acceptable as a proof of efficacy. In addition to general methodological reasons to refuse this approach, there are substantial differences between placebo patients in the different trials and it is unclear how to ensure comparability of any selected population to the existing historical series.

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. The use of non-inferiority active control trials as a proof of efficacy will raise difficulties as the effect size in terms of reduced relapse rate of currently authorised product is rather modest. Under these circumstances, a reasonably defined non-inferiority margin will be so small that the trial in practice will be close to a conventional superiority trial. If, however, a non-inferiority study is performed, the effect of a putative placebo must be considered as outlined in the CHMP guideline on the choice of non-inferiority margin (CPMP/EWP/2158/99). In any case, it is of major importance to include only patients with disease activity at least as high as in the historical studies for the comparator. With respect to disability, non-inferiority results cannot be interpreted.

Three arm studies with placebo, test product and active control are a preferred design but feasibility of long term placebo controls have become seriously limited due to the evidence of efficacy of available treatments.

A second option is to compare the new treatment to placebo in a short duration trial (e.g. one year or until patients have a new relapse) and thereafter to switch placebo patients to a predefined active treatment or randomise them to the experimental product or a predefined active treatment .

If the product is to be used in combination, a placebo controlled trial of 2-3 years 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 three arm trial seeking superiority of the combination versus both products in monotherapy.

In order to interpret comparison between monotherapies it is important to ensure that there is no selection of patients having shown non response (or suboptimal response) to previous therapy with the standard product.

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 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.

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 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.

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 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.

At the time of marketing authorization, 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 multiple sclerosis 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.