European Medicines Agency

London, 16 November 2006
Doc. Ref. CHMP/EWP/438043/2006

OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON MULTIPLE SCLEROSIS

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	European Charcot Foundation	
2	Biogen Idec	
3	Sylvia Lawry centre for Multiple Sclerosis Research	
4	German, Austrian and Swiss Multiple Sclerosis Therapy Consensus Group (MSTKG)	
5	EFPIA	
6	Amgen	
7	TEVA Pharmaceuticals	
8	Merck Sharp & Dohme	
9	Serono	

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 60
E-mail: mail@emea.eu.int http://www.emea.eu.int

Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW		
Clarification is needed with respect to: – Differentiation between Clinically Isolated Syndrome (CIS) patients and patients with an initial clinical attack and diagnosis of MS (McDonald criteria) as well as recommendations for inclusion in pivotal clinical trials, indications to be obtained, appropriate efficacy end points and duration of trials vs. placebo, taking into account that they are less likely to progress in disability than RRMS patients. – Differentiation between sustained accumulation of disability in RRMS and progression of disability in SPMS or PPMS, with questions on the acceptance of an effect on relapses as a valuable efficacy outcome in patients with SPMS.		
Suggested changes and anticipated problems with the proposed pivotal trials for efficacy in relapsing MS due to known difficulties with 2-year placebo controlled trials or superiority vs. active treatments. – Proposal to accept proportion of relapsing patients instead of the annualised relapse rate, allowing the switch from placebo to active treatment in those patients who relapse after having completed at least one year of treatment. – Comments on the particular difficulties with new oral drugs that do not intend to have superior efficacy to available parenteral but similar efficacy with a better profile regards convenience of administration or safety.		
Suggestions to expand and upgrade the MRI based parameters as surrogates for efficacy.		
SPECIFIC COMMENTS ON TEXT		
INTRODUCTION		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
page 4, alinea 4	Recent studies suggested that progression of lesions in MS might have, even in early clinical stages, two components: an active immunological aspect and a probably independent degenerative aspect.	Added to the text
Paragraph 4, line 2	Move the sentence in the 3rd paragraph and modify as proposed after the 1st sentence as it ‘s part of the MS definition and should not be associated to the CIS definition. The following sentence should be placed after “genetic predisposition”: **Nowadays, following the first clinical attack, the presence of new lesions in a second MRI is an accepted criterion for a diagnosis of MS**. Delete the sentence paragraph 4 “Nowadays, the presence of new lesions…in these patients”.	Sentence has been deleted as well as the term “classical” and “definite” associated with the diagnosis of MS

[1] Where applicable

Paragraph 3, line 5	Suggest differentiating relapse and clinical attack that could be used to describe the first clinical event, when "relapse" cannot. Suggest to replace “acute relapses” by **clinical attacks** along the text **(see the change in the attached guideline)**	Accepted.
2 SPECIFIC CONSIDERATIONS		
2.1.2	There is a confusion here between the term “progression of disability” simply as an increase of disability related or not related to the occurrence of relapses in the RR phase and the concept of "progressive phase” of the disease, which described a phase of the disease characterised by accumulation of disability independent from the occurrence of relapses. It is clear that separate approaches are needed to prove an effect of a drug in the RR phase with progression of disability compared to an effect in the progressive phase of the disease (SPMS). The PP phase of the disease equally demands a separate approach.	New wording including the suggested differentiation
2.1.3	**2.1.3 Improvement of an apparently stable residual disability** Progression of disability needs to be further defined or specified in terms of progressive phase. It is important to note, that the accumulation of disability seems independent from occurrence of relapses. Therefore it is needed to clearly separate approaches that are needed to be taken to prove efficacy of a drug in RR phase with progression of disability versus efficacy in progressive phase of the diseases	Included in section 2.1.2
2.2	**Treatment of acute relapse to shorten their duration and/or severity of symptoms and/or preventing their sequelae** We would like to stress here that treatment of the acute relapse and diminishing its severity is an important goal in MS patients care. Recovery from a relapse may take weeks to months. It is suggested that measuring Gadolinium enhancing T1 lesions should be included as outcome measure	Duration of at least 6 months will be maintained as a recommendation MRI (Gd enhancement) is proposed as a secondary end point in order to inform on duration of inflammatory activity
2.2	MRL would like to point out that the requirement for at least 6 months follow-up will be very difficult to implement in practice and could potentially result in a significant delay in the development of new therapies. MRL therefore suggests a 2-3 month follow-up period.	
2.2	- There are no rescue treatments for the recovery of a relapse. - The recovery phase from a relapse takes weeks or months. Even the 6 months period may be to short. Here the introduction of MRI to indicate the duration of Gad enhancement as a sign of inflammatory activity may be necessary. It is demonstrated to be superior to clinical evaluation.	

	2.3.1 Relapsing multiple sclerosis *"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 trials may raise problems…."* Although the effects of currently available disease modifying drugs (DMD) on relapse rate may be considered "modest", this effect has been shown consistently and uniformly as a significant treatment effect throughout numerous trials. It is correct that the influence on disease progression has not been shown in all of the pivotal trials of the currently approved DMD's. However, several reasons including trial design, power of the study and differences in primary and secondary outcome measures at that time may have contributed. However, we disagree that a clear demonstration of non-inferiority with regard to two clinical outcomes, i.e. significant influence on relapse rate plus influence on disease progression would not be sufficient for the approval of a new agent in the therapy of MS. It should be noted, that especially the interferons and glatiramer acetate, which represent the key DMD's in current clinical practice, are inconvenient in its application and – despite overall good tolerance, not without significant adverse effects and problems for the patient. Therefore, drugs with comparable (= non-inferior) efficacy, but a better mode of application/better profile of acute and long term adverse effects, would be a significant improvement for the care of MS patients in daily clinical practice. It is appreciated that placebo-controlled trials have predictable problems, especially in countries where approved DMD's are broadly available. We feel that for trials in relapsing-remitting multiple sclerosis, the placebo arm should not exceed a duration of 6 months and asymmetric randomization should be recommended. Otherwise, very strict escape rules have to be proposed in the study protocol. One possibility would be an informed reconsent after each clinical relapse or after confirmed EDSS progression. In European countries where currently available DMD's are broadly used, placebo-controlled trials in "selected populations", such as those refusing treatment after being well-informed about available therapies or those where benefits of current therapies are "less clear" may nonetheless raise ethical problems. It is not clear how these populations should be clearly elected. Performing placebo-controlled clinical trials only in countries where the participation in such a study is the only option to receive DMD's is another critical ethical issue and may lead to additional problems in selection bias, as well as quality of MS trial methodology which is the experience of all of us arising from study board activities.	
2.3.1 6th alinea	The effect on relapse rate should not be investigated in patients with any form of relapse (see comments on 2.1.3). There are many reasons to exclude placebo controlled trials in RR and CIS patients - the availability of active treatments - the possibility to recruit patients only in countries where immunomodulatory treatments are not available - the non-representativity of the included patient population - ethical consideration. However there are some reasons to include placebo controlled trials in the study of RR or PP Multiple Sclerosis treatment: - only a few disease modifying drugs are approved for MS	

	- a high number of patients do not reach to immunomodulatory treatment - MRI and clinical “red flags” can now be used to prevent patients to remain in the placebo-arm for too long. Clear indication should be given concerning the principle of “small numbers of patients” (see Baquato et al. Arch.Neurol.2005, 62:1684-1688). If selected population are used the results of a study cannot be generalised.	
	We agree with the assessment that purely placebo-controlled trials over a long duration will become more and more unacceptable. We appreciate the position of the CHMP to consider also innovative designs. However, it would be helpful if the guideline could elaborate, in a more detailed way, which short-term outcomes would be acceptable to demonstrate superiority of a new product over placebo in the given example of the 3-arm trial (see bracketed example in the guideline), e.g. imaging outcomes or relapse rate. Furthermore, it would be helpful if an acceptable duration of treatment for generating such short-term outcomes could be defined (major comment).	
2.3.1	The CIS patients are by definition not included in the diagnosis MS.	Agreed. New wording in this section referring to patients with a single clinical attack complying with McDonald criteria as MS patients. The term CIS refers now only to patients without McDonald criteria and it is accepted as an additional indication.
2.3.1.1	Definition of the CIS population that is not considered appropriate for demonstrating efficacy in MS is unclear - particularly with regards to the level of MRI activity. Are patients with CIS with supportive MRI that only partially meets the McDonald criteria considered an appropriate population to study in clinical trials i.e. those at high risk of developing MS? Please also confirm the position regarding separate indications in CIS populations. (Major comment)	
2.3.1.1	**Clinically isolated syndrome** The guideline committee asks for “*a demonstration of efficacy by means of decrease of accumulation of disability or at least a meaningful and sustained decrease in relapse rate within a 2 or 3 years’ time*". While we agree that a demonstration of significant influence on relapse rate over at least two years is mandatory, we would anticipate problems in formally demanding the demonstration of a significant influence on prevention of disability progression in this specific population, since trials throughout the last years showed that progression by means of EDSS is very low (or absent) within the first two (or three) years after a first demyelinating event (only 15% of CIS have EDSS greater 2.5 after f/u of 3-4 yrs). We would also propose to implement the issue of placebo controls in this population. We feel that trials attempting to demonstrate the effect of an agent in patients with clinically isolated syndrome, the entrainment of the placebo control arms should not exceed one year (12 months). Exceptions may include very strict escape criteria based on the occurrence of a clinical relapse or the demonstration of MRI progression. *“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.”* The meaning of this sentence is not absolutely clear to us. Clinically isolated syndrome by definition means that multiple sclerosis according to the McDonald criteria are not completely fulfilled, and that criteria demonstrating the dissemination in time (either clinically or by MRI) have yet to be demonstrated.	Agreed. Disability is downgraded to secondary endpoint and relapse rate is set as the primary endpoint 2-year placebo controlled trial allowing the switch to active treatment in case of a second attack is a feasible design.

3.1.1, 2nd alinea	The use of accumulation of disability in a CIS population is not advisable as a parameter because the lower levels of the EDSS scale do not measure disability. Only 15% of CIS patients have an EDSS > 2.5 with a follow-up of 3-4 years. The duration of trials in CIS population should be maximal 2 years, because in longer duration placebo control is not acceptable. It should be stressed that starting treatment at a very early point of time in the CIS population is an important strategy.	Terms have been clarified at the NfG
2.3.1.1 paragraph 3	The guideline states that "Clinical trials in these patients [CIS] should be long enough to address both the absolute efficacy of the product and the benefit vs. deferred start of conventional therapy for clinically definite MS". It is unclear if the guideline is suggesting that both these things need to be looked at within the same trial or if the latter can be done by comparison to historical data. If it is the former, can the guideline provide guidance on how such a study might be designed? Deferring the start of conventional therapy for clinically definite MS without a strict re-consenting process raises ethical concerns (major comment).	Clarified at the NfG. It is proposed to add a 2-3 year follow up of all patients, including those switched to active treatment after second attack or end of controlled phase.
	2.3.2 Primary progressive MS The statement that PP patients do not show high interpatient variability is incorrect, especially in terms of disease progression.	Agreed. Sentence deleted
	PP patients also showed high interpatient variability.	
3.2.1. paragraph 3	The annualized relapse rate (as opposed to time to second clinical event) is appropriate as the primary efficacy parameter in studies of CIS patients who meet McDonald's criteria only when effectiveness has not been previously demonstrated in the definitive relapsing MS population. In the case of CIS patients being studied as an additional and separate population to relapsing MS patients (in which the standard recommended efficacy parameters are assessed), time to second event or rate of conversion to CDMS is relevant as a primary measure of efficacy.	Not changed. A delay in time to second event does not necessarily imply a relevant clinical benefit..
3.2.1. 2nd line	**Primary efficacy parameters** Primary efficacy parameter in SPMS should be disability not relapse rate	This was also the view of the EWP. Section reworded to make it more clear
	The primary efficacy parameter in SPMS should not be relapse rate.	
4.1 paragraph 4	Measuring time to progression using EDSS has certain downsides. EDSS scores are determined at pre-defined points in time and hence the time measurement will not be continuous but more of a "step-function". An analysis of the proportion of responders/non-responders at each time point could be seen as a more appropriate efficacy measure. Could the guideline comment on whether this is acceptable? (major comment)	
4.1 paragraph 5	It is suggested that the number of relapses per X patient years could be measured as this allows for patients to have greater than one relapse and does not group data - i.e. keeps more information in the summary measure. Could the guideline address this point? (Major comment)	

4.3 Magnetic resonance imaging	*"Therefore Magnetic Resonance Imaging is not a validated surrogate end point for clinical outcome in pivotal studies."* Albeit we agree that MRI is not acceptable as a primary outcome measure in pivotal studies, we would disagree that MRI is not a "valid surrogate endpoint" for clinical studies. The vast majority of studies throughout the last years have shown a clear correlation of the influence of MRI measures with clinical parameters, therefore the chosen expression/phrase seems too strict.	Reworded
4.3 Magnetic resonance imaging	There are many recent clinical trials and studies demonstrating that brain atrophy is an accurate and reliable measure of brain damage in MS. The correlation of progression of brain atrophy with the progression of disability in RR has been demonstrated. On the contrary the correlation decreases in the SP phase of the disease. Atrophy measures, active lesions, T1 and T2 lesion load are very important secondary end points. They are objective measures and may contribute significantly to the internal consistency of the findings. In phase III clinical trial clinical measurement should remain the primary end point.	
	5.1 Diagnostic criteria It should be included that the revised McDonald criteria (Polman et al. Annals of Neurology 2005) should be used.	Agreed
	6.5 Confirmatory trials *"Efficacy should be demonstrated by means of a superiority trial versus Placebo or any available single therapy either in terms of relapse reduction and prevention of accumulation of disability."* As indicated above, the demand of "superiority" is difficult to argue, not only from a clinical standpoint. For example, the only approved therapy for progressive forms of multiple sclerosis is mitoxantrone. This agent has a number of severe adverse effects including the strict limitation of not overcoming a specific cumulative dose due to risk of cardiotoxicity. With regard to a drug that has a number of limitations in terms of long-term use etc., any drug with a non-inferior efficacy would be advantageous for the patient and the caring physician. This is especially true in a patient group (progressive MS, patients that failed/insufficiently responded to baseline treatment) where other treatment options are not available. Therefore, we would suggest to revise the guidelines in a way that in trials assessing the effect of a substance versus an active comparator, **non-inferiority** may be sufficient for an approval, given that the drug has significant benefits for the patient and the doctor (adverse effect profile, mode of application etc.).	There is some confusion between two different ideas, referring to 1) the benefit risk assessment and 2) demonstration of efficacy in pivotal trials: 1. It is agreed that a new product with similar efficacy as compared to standard therapies could be approved, moreover if it has better profile with regards to safety or convenience of administration. 2. Trials with a non-inferiority design have known limitations, as the means to demonstrate efficacy and, those limitations are particularly present in this field. It is clarified that some proof

		of efficacy should come from a superiority trial although a magnitude of efficacy similar to available therapies could be enough to get an approval.
	7.1 Organ specific adverse events *"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."* We agree that judging organ specific adverse events is a valid point. In clinical trial practice this may nonetheless be hard to realize, specifically in case of those patients who would like to stay on the drug after reaching the pre-defined end of treatment. This option has traditionally been offered and serves as an invaluable element to document/follow up patients in order to assess the long-term safety of investigated drugs. Therefore trial designs should include the requirement to achieve information on clinical/MRI rebound in a meaningful number of patients receiving active treatment (but not dictating discontinuating treatment in the complete active study population). This may be sufficient to assess clinical and/or MRI development after discontinuation of active treatment.	Agreed. Reworded