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EMEA/CHMP/EWP Workshop:

Slowing the Progression of Neurodegenerative Diseases: Medicinal Products (MP) Clinical Development London, 2 October 2006

Introduction

New European pharmaceutical legislation (EU Regulation 726/2004) was enforced in November 2005, and Neurodegenerative Diseases (NDG) are among the four therapeutic areas currently included under the mandatory scope of the centralised procedure.

Where Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease (PD) and Alzheimer's disease (AD) largely differ for their clinical implications and course of disease, all are basically provoked by progressive loss of neurons, which affects different neuronal systems at different speed, giving raise to the loss of related neural functions. These three diseases have been considered as representative examples of NDGs for this first EMEA Workshop. Then, particularly for AD and PD the number of patients concerned is relevant, with an increase in prevalence expected over the next coming decades in parallel with the elderly and very elderly prevalence increase in Europe and outside.

Over the last 2 years frequent and wide ranging discussions on ALS, PD and AD took place within the EMEA, mostly within the Scientific Advice and the CHMP Efficacy Working Party, and often triggered by the Industry in the frame of new medicines development issues.

New therapeutic strategies for slowing the progression of neurodegenerative diseases represent an inevitable focus of these discussions, as innovative research and technological advances may now provide avenues to develop medicines specifically targeting the mechanisms underlying neuronal death, and should be used in the early stages of disease to get the most benefit. These medicines are also called disease modifiers (DM).

But, the area is complex with many unresolved development issues and effective and safe medicines will only reach the patient via a co-operation and a sharing of expertise/insight between academia researchers, industry developers and regulatory authorities.

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Executive Summary

Within the Neurodegenerative Diseases area, a disease modifying medicine (DM) is broadly meant halting or delaying the neuronal loss therefore slowing the progression of neurologic symptoms, and indeed modifying the clinical known course of the disease.

While significant progress in disease knowledge is continuously achieved (both on the underlying pathology and clinical assessment methods) how the current knowledge can translate in operational criteria in order to efficiently develop disease modifiers, still needs to be univocally defined across industry, academia and regulators.

Very early stages of disease theoretically identify the target population of all neurodegenerative diseases. In fact, when a good number of neurons are still viable, effective treatment could result in meaningful preservation of neurologic functions, like cognitive abilities in the case of Alzheimer's disease. Even a measurable slowing of the expected deterioration rate could be considered a clinically relevant therapeutic objective.

While DM drugs should theoretically be introduced as early as possible, in a clinical setting it is more feasible to detect significant therapeutic effect at the apex of disease activity.

Moreover very early stages of ALS and AD are particularly unstable, hopefully a proportion of patients actually stabilize or even revert, and this low predictability of the clinical course implies a limited capacity to set up statistical hypotheses to be verified in controlled clinical trials. Early stages of AD or even 'pre-AD' have been targeted, but unsuccessfully at the moment, one of the problem being that there is not a well defined and validated way of diagnosing these patients.

Equally important the potential benefit of exposing such early patients to the candidate medicine is counterbalanced by the potential risk to induce untoward effects in reasonably "healthy and functioning" people, who normally would not seek medical help, like in the pre-clinical stage of Parkinson's disease.

Time to reach "milestones clinical symptoms" (i.e. Hoehn &Yahr stage III in advanced PD) remains the most reliable way to compare investigational medicine to placebo. No medicine has yet been approved as disease modifier, so no reference comparative treatment is currently available in AD and PD. In ALS, riluzole is the only medicine centrally approved, it can be regarded as disease modifier and is the reference treatment to date. Nevertheless, the observed therapeutic benefit of riluzole is quantitatively low and new medicines are requested to do better.

"Survival" curves models may be used based on these milestones. Death is an acceptable endpoint for ALS but is not the most relevant for AD or PD.

Clinical trials based on slope analysis (comparison of decline rate of a clinical outcome) can also be used, however they present a number of limitations, including the imputation of missing values or withdrawals and the necessary number of points of measurement over time.

An additional problem is the use of scales as endpoints that are also used to show a symptomatic effect, as for a "true neuroprotection claim" it has to be shown that the effect is not symptomatic. In practice endpoints for DM and symptomatic treatment are not different and is rather the duration of effect over time with the consequent long lasting clinical benefit the main focus for disease modification.

The use of biomarkers (neuroimaging, biochemical markers) as surrogate endpoints could reasonably circumvent one of these aspects, as far as the correlation with primary clinical endpoints could be proved. The value of biomarkers in phase III pivotal studies is not yet established. To date, no validated biomarkers have yet been established for AD or PD, whilst in ALS clinical endpoints remain the most relevant objective of a clinical trial.

Biomarkers may also be used to better target these subjects who unequivocally will face the full-blown disease, thus limiting the exposure of spontaneously remitting patients, etc. At present, biochemical markers or genetic markers can help to identify patients who will develop AD, but still does not give sufficient information on the expected time course of disease.

In the case of AD, the use of neuroimaging techniques may effectively contribute to identify patients with an underlying cerebral atrophy (MRI), measuring the glucose metabolism of functionally affected cerebral areas (FDG PET) or reveal and quantify the extent of amyloid deposition (ligand PET). Patterns of changes (at MRI and PET) may be predefined both for diagnostic purposes and in order to stage disease progress overtime. As mentioned above, the correlation between neuroimaging changes and therapeutic outcomes, is yet to be proved.

While at present the role of these innovative techniques for regulatory claims is not yet established, it is valuable for the three neurodegenerative diseases we discussed, ALS, PD and AD, to pursue the research on innovative techniques both for detection of underlying pathology and therapeutic outcome as well as to make available new data to the whole scientific community in the shortest delay.

Efforts are ongoing to better define preclinical stages of PD and AD and this could lead to an update of diagnostic criteria for AD. Updated criteria will undergo a period of clinical validation before to be integrated in regulatory guidelines.

In conclusion the workshop brought up the opportunity to exchange expertise between Academia and Regulators across the three diseases, to focus and define common tasks in disease modifiers development, to underline the methodological specificities and acknowledge the state-of-the-art for each disease.

The EMEA plans to continue the debate on disease modifiers in 2007, looking forward to incorporating new research data from the Industry and the Academia, and opening the debate to the Patients i.e. upon clinical relevance of effects and acceptable levels of risk.

Objectives of the Workshop

Within the Neurodegenerative Diseases area, a disease modifying medicine (DM) is broadly meant halting or delaying the neuronal loss therefore slowing the progression of neurologic symptoms, and indeed modifying the clinical known course of the disease and delaying disability. Compensatory mechanisms and their failure may also affect the course of disease.

Based on the current understanding of the underlying pathology and of the clinical time course of each disease, the discussion would attempt to:

- Define the optimal patient population for demonstrating disease modification.
- Identify meaningful clinical endpoints to assess disease modification.
- Clarify how biomarkers and neuroimaging can contribute to the development of disease modifiers medicines, and later integrate into the treatment and management of the disease.

Specifically the group was requested to consider where the key knowledge gaps exist and see what scientific and development approaches are currently practical and what is purely theoretical. In the end it was hoped that the workshop would improve the respective understanding on how to plan and execute clinical trials to gain the approval of a safe and effective disease modifier (for a defined patient population). It should also generate novel debate within regulatory environment and produce information available to scientists and the general public, *for whom this document is intended*.

NDG Disease comparison

	ALS	PD	AD
Understanding and definition of **Patient Population**	High	Medium	Medium
Clinical Course	Short	Long	Medium
Disease Progression	Aggressive	Medium	Medium
Unmet Therapeutic Needs	High	Medium	High
Efficacy of Therapies	Low	High	Low
Availability of robust Outcome assessments	Medium	Medium	Medium
Availability of Biomarkers	Low	Medium	High
Predictiveness of Biomarkers	Low	Low	Medium
Number of Medicinal Products currently in development	Medium	Medium	High

Amyotrophic Lateral Sclerosis (ALS)

Disease Profile

ALS is thought to be one NDG disease where *disease modification* could result in direct improvement of survival, in that it could succeed in preventing the destruction of the neurons innervating the diaphragm, and the consequent respiratory distress.

Riluzole is the only established therapy. It is admitted that it has some DM properties, nevertheless the size of improvement versus placebo is relatively small, and there is an urgent need for more effective therapeutics.

Although ALS is a multi-systemic disorder of the brain the anterior horn cells are identified as a key potential target of therapy. However, it will not be mandatory for a disease modifier to show to be able to act on the pathophysiological mechanism as a prerequisite (mechanistic action). ALS animal and cell models are currently not seen as being highly predictive, therefore the clinical proof will come first and with the simplest trial design.

The methodological approach to ALS differs in many ways from the ones in Parkinson's and Alzheimer's.

Patient Population

This is well defined with phenotype and prognosis classified according to the *El Escorial* scale: Definite, Probable and Possible ALS accounts for 75% of the patient population.

Additional divisions are 'classical' vs. early and familial (5%-10%) vs. sporadic (90%-95%). There are a large number of prognostic factors including age at onset, referral delay, gender, weight, EE Category, bulbar v. limb forms, etc…

Both definite and probable ALS are eligible to controlled clinical trials (CTs) and coincide with the target population. In facts, to date it is not sufficiently proven whether earlier stages may significantly benefit from treatment, due to the high variability of the early clinical course. Nevertheless no specific exclusion criteria were identified.

Presently there is no role for biomarkers in the choice of the study population, which mostly relies on clinical basis.

Clinical Endpoints and Study Design

Available outcome assessments include: functional scales; muscle strength, respiratory function and other physiological measures; overall survival or equivalents (time to respiratory assistance). Commonly applicable outcome measures (like muscular strength) do exhibit linear decline that would allow slope analysis, whilst the survival analysis remains the established approach. To use the delay of the transition from one stage to a more advanced stage is debatable.

Because non-invasive respiratory assistance and invasive respiratory assistance significantly prolong time of survival, scales measuring Quality of Life should also be used and taken into account for establishing the therapeutic benefit.

Because numerous factors influence the clinical outcome (age at onset, clinical sub-type, etc.), stratification is needed. However, over-stratification was felt to be potentially detrimental as it may lead to a dilution or masking of the clinical efficacy. Centre effect does definitively play a role and must be considered.

Focus of scale use is likely to change according to the development phase. In Phase II when proof of concept is trying to be demonstrated then functional scales, such as ALSFRS-R, may be appropriate. ALSFRS-R can be completed by phone by the patient, is reproducible and reliable and allows slope or time to event analysis.

In Phase III when long-term outcomes must be demonstrated then a combination of functional and survival (primary) endpoints are required.

Depending on the endpoints and on the difference that we expect to find between groups, 18 months would be a suitable duration for a CT, to be adapted.

Biomarkers

Potential biomarkers include: NoGo A, MR Spectroscopy, DTI and Proteomics.

To date no biochemical or neuroimaging markers are validated. No reliable surrogate markers have been identified and clinical endpoints remain essential

Reference treatment or Placebo controlled trials?

Add-on to riluzole is the standard study design in order to preserve the maximum therapeutic potential during long-term trials. Direct comparison to placebo may be possible depending on the target population. Some questions were posed about whether a sequential trials design was possible in order to demonstrate efficacy more easily and still deliver treatment. Probably this kind of issues needs to be solved on a specific case basis (mechanism of action, expected size effect, expected safety profile).

Ongoing clinical trials

While no other drug was approved after riluzole (2001) in the EU, several products have undergone clinical development. Three compounds had received orphan medicine designation, but none of these have entered the centralised procedure yet.

Parkinson's Disease (PD)

Disease Profile

With the longest time-course among the three NDG diseases we debated, PD is a complex disease with multiple neuronal populations involved in sequence. The first and more prominent system is the dopamine regulated sub-cortical group of nuclei (*substantia nigra, striatum, etc.)* that control the extrapyramidal nervous pathway (involuntary movements).

Seems to be a clear and well defined disease progression: development of cardinal motor features, evolution of treatment related motor complications, non-dopaminergic motor impairment, evolution of non-motor symptoms, progression of global disability and possibly dementia. Milestone symptoms scatter the phases of disease, like the appearance of balance problems or reaching Hoehn &Yahr stage III.

Progressive decline of motor scores is greatest in early years as a result of significant loss of nigral neurones. Decline at the UPDRS (unified Parkinson disease rating scale) is considered linear with a rate of approximately 9 points per year in untreated patients.

The rich array of currently available symptomatic therapeutics strongly altered the understanding of the natural course of the disease. Dopamine replacement treatment (L-dopa, etc.) dramatically improved survival and gradually revealed (after the initial pure dopamine responding set of symptoms) a true multi-systemic neurodegeneration, encompassing the decline of noradrenergic and serotonergic sub-systems, autonomic dysfunction and eventually including dementia.

Regarding possible disease modifying medicines for PD, taking into account the multifactorial nature of the disease, putative 'neuroprotective' agents identified via pharmacologic activity on single pathogenetic steps (*in vitro* or *in vivo* animal models) could not be easily translated into clinical meaningful outcomes.

It is plausible that the concept and understanding of PD clinical progression had evolved over the years due to constant and consistent use of symptomatic therapies. It was also argued that current L-Dopa therapies might have some level of disease modifying effect.

This obvious consideration would imply a flaw in the definition of "disease modifier" as L-dopa, is basically a symptomatic treatment, not altering the rate of dopaminergic neuronal loss. In the end, key to disease modification in Parkinson's is to slow down the rate of progression and produce an effect 'that lasts', postponing disability and dependence.

While a probable mechanism of action should also be demonstrated, it was certainly felt that any disease modifying effect in PD will focus on showing a relevant and persistent effect on disability.

Patient Population

In view of a disease modification approach patient population seems to be arbitrarily divided into: At Risk, Early Disease (untreated, treated and stable) and Advanced disease (motor complications, 'non-dopaminergic' motor features, non-motor features).

At Risk Population – Clinical epidemiology studies are currently investigating the predictive value and natural course of PD pre-morbid status. This is still an experimental category. Pre symptomatic patients could be identified on the basis of PD familiarity, RBD (a sleep disorder), tiny elements like hypo/anosmia (loss of smell ability), traits of (anancastic) personality, low-caffeine and non- smoking habits, accompanied by echographic abnormalities in the cerebral stem. Insufficient data availability and clinical characterisation make this group currently non-eligible for CTs. No therapeutic need has been identified to date (no-expected-benefit population).

Early Disease - Dopaminergic neuron loss is thought to be more rapid in the earlier phases of disease with a linear decline of motor function. Recently diagnosed patients belong to the category and are eligible for CTs.

Advanced Disease – Later in the course of disease the loss of motor function seems to plateauing and the clinical course is rather scattered by non-dopaminergic symptoms milestones, like loss of balance control and consequent falls, significantly impacting Quality of Life. Patients are considered still eligible for disease modifying CTs, with medicinal products aimed at preventing further neuronal loss.

Clinical Endpoints and Study Design

In *Early Disease* linear progression rates (equal about 9 points on the UPDRS score) provides the basis for a *slope analysis* approach to assess medicine efficacy; several study designs exist and have already been implemented in clinical trials.

In *Advanced Disease* it seems most appropriate to use *survival analysis* (time to a mile stone clinical event).

Therapeutic goals, timeframes and endpoints will be different for each stage of the disease.

1. Early untreated PD: the goal is to slow progression of cardinal features by assessing change in UPDRS, or time to L-Dopa/DA-agonists. Caveats concern the use of time to L-dopa, as a highly standardised approach would be necessary. The proposed trial duration is from 9 to 24 months.
2. Stable treated PD: the therapeutic goal are to slow further decline of motor impairment, progression of disability, prevent motor complications and prevent non-motor complications. Studies may demand 2-5 years. Felt that key outcomes measurements for this stage could be the emergence of so-called axial symptoms: e.g. freezing of gait, loss of balance or Hoehn & Yahr stage III.
3. For advanced PD prevention of disability become the key therapeutic goal. Clinical endpoints are also wide-ranging including; autonomic failure, falls, cognitive symptoms and possibly 'time to' dementia and time to nursing home placement.

However, dementia applies to a sub-group of patients and nursing home placement is not standardised across the EU. Due to the excellent life expectancy of PD patients, the overall survival is no more an efficacy end-point, except for excluding over-mortality. Clinical studies for this population could extend over five years.

Concerning trial design, it was felt that the following factors should be taken into account:

- Parallel design
- Time to endpoint or to progression should be assessed. Wash-in and wash-out designs may be valid to demonstrate DM, but more data are awaited.
- Symptomatic medications in PD work well therefore they should probably be included in trials, except for very early PD. An add-on strategy should certainly be considered in advanced PD.
- The randomised withdrawal design was specifically discussed during PD session. If medications are to be washed out, what is the optimal duration to do this over? *Many panellists suggested two weeks would be long enough, but others suggested much longer intervals, up to 2 months.* It was felt that wash-out duration has to take into account the known characteristics of the investigational drug, not only pharmacokinetic but also pharmacodynamic durations and this could involve as well compensatory mechanisms.
- Long-term follow-up will always be required.
- Data could be analysed as time to event or percentage of patients reaching a milestone; comparative rates of progression (slope analysis) may be a methodological approach provided adequate consideration is given to what constitutes a clinically relevant difference at end.

Requirement for different trial design, outcomes and endpoints depending on whether trial is Proof of Concept (POC) or long-term phase III efficacy study.

Biomarkers and Neuroimaging

A number of options are currently available including functional assessments, biochemical assessments and imaging.

Dopamine transporters or precursors of dopamine can be visualised by PET or SPECT, giving an estimation of neuronal reserve.

While the use of biomarkers as surrogate endpoints could theoretically overcome the difference between symptomatic effect and disease modification in PD, the correlation with primary clinical endpoints is lacking. In facts, currently available data collected during l-dopa or dopamine agonists' treatment are conflicting. So far there is discrepancy between clinical improvement and rate of neuronal loss as estimated by neuroimaging. Further limitation is in that the above imaging techniques are not predictive for non-dopamine related symptoms.

Nevertheless it was felt that the study of biomarkers should be pursued: they could possibly show more correlation in the pre-clinical stages (at-risk non-benefit population). Most of all they could concur to dose-finding definition. In conclusion it was suggested that

neuroimaging techniques should be routinely used as a secondary outcome measure in clinical trials, in order to collect sufficient data for surrogate endpoint characterisation.

Reference treatment or Placebo controlled trials?

To date no disease modifier medicine was approved in EU, therefore placebo remains the reference treatment for phase III CTs.

Nevertheless, the richness of therapeutic options and the current therapeutic practice favouring polytherapy, makes largely unpractical to assess the efficacy of a single agent versus placebo, except in early or very early stage.

In advanced disease add-on designs to pre-existing stable therapeutic regimen are accepted, comparing the investigational drug to placebo.

Alzheimer's Disease (AD)

Disease Profile

- Dementia of the Alzheimer's type may be viewed as the final step of a long lasting pathologic process spanning over decades. Symptoms are thought to emerge and make clinical diagnosis feasible only when several compensatory systems failed one after another. At that point the typical cognitive deficit, memory complaint, and at least another intellectual disability will create impairment in social functioning and declining effectiveness in everyday life activities. See also NINDS-ADRDA criteria.

- Current therapies are symptomatic treatments with low efficacy. In fact, in spite of substantial research efforts put in place, currently available medicines only slightly improve symptoms over a limited period of time and eventually do not modify the clinical course of disease.

- Current neuropathology understanding of AD is largely based on the amyloid cascade hypothesis and amyloid deposition progressively spreading across the cortex. Other typical lesions are neurofibrillary tangles. Nevertheless AD pathogenetic mechanisms are far from a causal demonstration and many factors, including hereditary susceptibility (as for Apo-E4 allele) and microvascular lesions possibly related to pre-existing diabetes and/or hypertension, may play a role. In fact the overlapping with vascular (specifically microvascular) lesions frequently found at autopsia of otherwise clinical AD cases, may weaken the putative correlation established between the extent of amyloid pathology and the emergence of symptoms.

- Fairly clear clinical progression over a few years: emergence of initial cognitive symptoms, most of the time an amnestic deficit for delayed recall of words or images, other cognitive deficits and steady loss of instrumental activities, deterioration in progressively more cognitive and functional domains, behavioural abnormalities, eventually leading to nursing home placement, loss of self-care, death.

Patient Population

- Two groups were specifically discussed for disease modifying programs: Established disease (moderate AD) - standard diagnostic criteria for dementia of the AD type (according DSM IV and according the NINDS-ADRDA) currently identify the reference target population for clinical trials, based on the fact this is the more predictable phase of disease, as exemplified by approximately *8-point* loss at the ADAS-Cog over 1 year.

- As for Mild AD- the rate of progression is less characterised than for moderate disease and less clinical data are available, nevertheless this group is probably the most relevant target for DMs.

- Prodromal stages- as the neuropathological correlates of AD may begin 15-20 years prior to manifestation of dementia, prodromal stages would provide in theory and excellent

opportunity for therapeutic intervention. In practice, in spite of relevant investments in clinical epidemiology and the realisation of numerous therapeutic trials, it is clear that prodromal stages of AD are not fully characterised to date. Particularly, distinction from 'normal aging" is uneasy (population norms are difficult to use) and time to significant worsening into true dementia is difficult to model and predict.

While some clinical features –as the amnestic complaint specifically affecting delayed recall abilities – are very suggestive of an underlying AD pathology, they do not identify univocally a specific population undergoing a typical clinical course. In fact reversion to normal status is frequent (20-40% of the cases according to several sources), and the therapeutic need to treat elderly people with an isolate memory complaint is questionable.

Nevertheless suspicion of AD may be further corroborated by the detection of biochemical markers in the cerebro-spinal fluid (CSF) (these are abnormal peptides related to amyloid deposition in the brain, or products of neuronal fibrils degeneration), and when a specific pattern of cerebral atrophy is observed using Magnetic Resonance Imaging (MRI), now a quite accessible and reliable *neuroimaging* technique. General atrophy but most specifically medium temporal lobe atrophy (which is closely related to memory functions) are the key changes.

However both time of onset and subsequent clinical course cannot adequately be predicted at this stage. This makes it currently unpractical to involve this very early population in clinical trials, including the ones for disease modifying medicinal products.

Encouragingly enough, a huge clinical research effort is currently underway, and more significant steps could be triggered by the availability of long-term clinical results. Diagnostic criteria of early/very early AD are currently under revision and will subsequently undergo a validation phase. They are expected to impact the current classification over the next two years.

Clinical Endpoints and Study Design

At present primary endpoints are clinically based.

Neuroimaging and biomarkers stay as co-primary in phase II studies only and are not acceptable as a proof of efficacy in phase III trials. At present it would be useful to measure them in phase II trials, to get more insight in correlation. *It cannot be excluded that positive results from large clinical trials could provide a different view in this discussion*.

Current guidance documents focus on assessment of symptomatic improvement: cognition (cognitive endpoint tests), activities of daily living (functional endpoint) and overall clinical response as reflected by global assessment (global endpoint).

Established disease (moderate AD) – The symptomatic effect currently observed with cholinesterase inhibitors is small (giving room for increased effect size with new medicines) and time limited (no lasting effects). As for the cognitive endpoint, ADAS-Cog rating scale is still considered a reliable option, where z-scores (composite cognitive outcomes) have not yet demonstrated their robustness in terms of clinical relevance or external validity. As for global/functional endpoints, global evaluation is quite a problematic endpoint (*CIBIC+*) and

both Activities of daily life (ADL) and instrumental-ADL (I-ADL) show weak correlation with cognitive outcomes and a non-linear behaviour. ADL are however the preferred co-primary endpoint, as they give insight in how an effect on cognition may translate in a clinically relevant outcome. In fact linearity remains a key feature for an adequate assessment tool to compare rate of decline. Response to a given treatment is better to be defined in the context of a specific development programme.

In prodromal stages, assessment tools are still in a research stage and regulatory requirements have not been established to date. Nevertheless it is becoming clear that norms based on "healthy elderly population" are not an adequate meter for quantifying cognitive deterioration and the "previous known performance" of the individual patient is a better indicator of meaningful cognitive decline.

The use of "conversion" to clinical dementia presents a number of methodological limitations. As for decline-rate measures, these are more promising when based on patient's previous performance – however is not clear if slope comparison clinical trials can achieve sufficient statistical power.

- *Might be* possible to demonstrate disease modification to some extent using established outcomes: e.g. ADAScog and IADL, slope analysis in long-term two period design trials (e.g. randomised withdrawal), but the outcome needs to be clinically relevant.

- Must be considered that decline in cognitive, or other domains of assessment, is not linear in the disease process and depends on severity of disease and assessment tools used.

- Longitudinal analysis ('Life-table') is considered as a way of analysing the effects of anti-dementia drugs. Despite potential benefits task is made difficult by lack of robust clinical endpoints and very complex and indiscreet progression events. There are pros and cons of all outcome measurements that must be assessed fully before inclusion.

- As in other diseases death is not a robust endpoint as most AD patients are elderly with significant co-morbidities. As already mentioned, overmortality has to be ruled out. Useless to say sufficient long-term data are to be made available at the time of filing.

Biomarkers and Neuroimaging

Numbers of biomarkers are currently available for AD:

- Structural MRI: measures volumetric changes of the whole brain, and medium temporal lobe structures (like the hippocampus) that are mainly involved in memory functions. This technique corroborates clinical diagnosis of AD by excluding major concomitant cerebral conditions and may give reliable information about differential rate of atrophy overtime.

- PET and other functional imaging provide reliable assessment of functional indices of the brain activity. FDG-PET measures glucose metabolism in different areas of the cortex; neurotransmitter function and ongoing pathological process like amyloid deposits; amyloid ligand PET measures the amyloid deposit in the cortex; functional MRI, MRS, etc. are also available.

- Biochemical: markers in cerebrospinal fluid (CSF): Aβ1-42 peptide, Tau and phosphorilated-Tau (p-tau) proteins. These biomarkers show fairly robust sensitivity and specificity for active AD pathology, which means that they offer the potential of a good predictive value. P-tau may be of particular value for the differential diagnosis of AD dementia versus other aetiologies. It is less clear in which extent modification in the pattern of these peptides in the CSF (reduction in Aβ1-42, increase in tau) may correlate to the clinical changes. As for longitudinal correlation with possible therapeutic outcome this has not been demonstrated.

- Genetic markers: like the Apo-E4 allele, may help to identify individual at increased risk to develop clinical dementia.

CSF biomarkers may consistently improve diagnosis of AD in its earlier stages, as a part of an integrated diagnostic work out.

It seems acceptable to exploit well-characterised biomarkers to identify "at-risk" subpopulations of patients and patients who will more probably respond to a given medicinal product. This includes genetic biomarkers, with the aim of reducing the number of patients to be exposed and improve the benefit-risk ratio. But at the moment there are insufficient data for this enrichment strategy.

Structural (volumetric) MRI seems to offer relative robustness. Brain volumetric changes closely parallel underlying pathologic changes in AD and reflect clinical worsening. MRI consent to exclude from clinical trails these patients where a macro-vascular component substantially concurs to clinical symptoms as well as other neurologic conditions. Its potential as a surrogate marker is based on the postulate that decrease in atrophy rate will correspond to decrease in clinical deterioration. It is hoped that pharmacological effects of disease modifying agents will be detected via differential rate of atrophy. Conflicting results were observed in a recent trial with an immunologic product. Standardisation among centres may represent a practical issue to overcome in large clinical trials.

It looks very important to pursue this line of clinical research on MRI, which is at present a very accessible and safe.

PET techniques, which visualise topography and extent of functional changes, could offer the advantage of higher sensitivity to pharmacologic effects. Glucose metabolism gives very useful representation of brain activity. Hypofunction in the medium temporal lobe closely parallels cognitive impairment in AD, etc. Amyloid burden tracing may be a sensitive diagnostic tool: a number of ligands, with some differences in terms of specificity and retention, are presently available and are undergoing to extensive clinical validation studies.

On the other hand these techniques are very lengthy and frequently quite demanding for the patient therefore small numbers can be tested.

No data are currently available on the longitudinal value (as surrogate markers) of -FDG- or amyloid-binding PET.

The ideal surrogate endpoint features:

- Changes induced by therapy on surrogate biomarker also reflect changes in clinically meaningful endpoint.

- Surrogate should have some basis in disease pathology and be able to contribute to explanation of therapeutic effect.

- Surrogate will be reliable enough to predict clinical outcome.

It was felt that robust biomarker data would be mandatory for successful outcomes studies in disease modifiers medicinal products whilst neuropsychological tests may be more appropriate for screening patients for trial inclusion. An integrated approach based on a combination of robust clinical evidence and biomarkers would be adequate in the context of a clinical development programme. More clinical research is encouraged.

Reference treatment or Placebo controlled trials?

No disease modifying medicinal products have been approved on the market to date for AD indication. AchI and memantine only account for symptomatic improvement. Therefore pivotal trials are placebo controlled.

Where add-on is in principle justified, taking into account we are dealing with small effects, and aiming to reduce the pharmacological background noise, monotherapy remains a good option. And not to be underestimated, simple placebo control may also allow better resolution of safety issues.

This bring up the problem of minimal duration for disease modification trials, that require much longer observation period than symptomatic treatment: a 2-year interval, is to be considered a reference value, to be weighted in the context of the overall methodological approach and implementation objectives of a given development programme.