# Regulatory Requirements for the Clinical Development of New Therapies for the Treatment of Alzheimer's Disease

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***We shall not cease from exploration***
***And the end of all our exploring***
***Will be to arrive where we started***
***And to know the place for the first time.***

T.S. Eliot

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AD | Alzheimer's Disease |
| AChE | Acetylcholine Esterase |
| ADAS-cog | Alzheimer's Disease Assessment Scale-cognitive subscale |
| ADCS-ADL | Alzheimer's Disease Cooperative Study Unit - Activities of Daily Living Inventory |
| ADCS-CGI-C | Alzheimer's Disease Cooperative Study Unit – Clinician's Global Impression of Change |
| ADL | Activities of Daily Living |
| ADRDA | Alzheimer's Disease and Related Disorders Association |
| ADRQL | Alzheimer's Disease-Related Quality of Life |
| Aph-1 | Anterior pharynx-defective 1 |
| APOE | Apolipoprotein E |
| APP | Amyloid Precursor Protein |
| BACE | Beta-Site Amyloid precursor protein-Cleaving Enzyme |
| BEHAVE-AD | Behavioural Pathology in Alzheimer's Disease Rating Scale |
| BGP | Behavioural Rating Scale in Geriatric Patients |
| b.i.d. | bis in die (Latin), twice daily |
| BRSD | Behavioural Rating Scale for Dementia |
| cAMP | cyclic Adenosine Monophosphate |
| CAS | Caregiver Activity Survey |
| CDK5 | Cyclin-Dependent-Kinase 5 |
| CDR | Clinical Dementia Rating Scale |
| CDR-SB | Clinical Dementia Rating Scale-Sum of Boxes |
| CFR | Code of Federal Regulations |
| CGI-C | Clinical Global Impression of Change |
| CGI-S | Clinical Global Impression-Severity scale |
| CHMP | Committee for Medicinal Products for Human Use |
| CIBIC-plus | Clinician's Interview Based Impression of Change |
| CNS | Central Nervous System |
| CPMP | Committee for Proprietary Medicinal Products |
| CSF | Cerebrospinal Fluid |
| DAD | Disability Assessment in Dementia |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EC | European Commission |
| ECG | Electro Cardiogram |

| | |
|---|---|
| EMEA | European Medicines Agency |
| EU | European Union |
| FAST | Functional Assessment Staging Scale |
| FDA | Food and Drug Administration |
| GAG | Glycosaminoglycan |
| GDS | Global Deterioration Scale of Reisberg |
| GSK-3 | Glykogen Synthase Kinase 3 |
| HIS | Hachinski Ischemic Scale |
| IADL | Instrumental Activities of Daily Living |
| ICD | International Classification of Disease |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IND | Investigational New Drug |
| JNK | c-Jun N-terminal Kinase |
| LBD | Lewy-Body Disease |
| MA | Marketing Authorisation |
| mg | milligramme |
| MMSE | Mini Mental State Examination |
| MTD | Maximum Tolerated Dose |
| NDA | New Drug Application |
| NINDS | National Institute of Neurological Disorders and Stroke |
| NMDA | N-methyl-D-aspartate |
| NPI | Neuropsychiatric Inventory |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| PD | Parkinson's Disease |
| PDE-4 | Phosphodiesterase-4 |
| Pen-1 | Presenilin enhancer 1 |
| Pen-2 | Presenilin enhancer 2 |
| PIP | Paediatric Investigation Plan |
| PREA | Paediatric Research Equity Act |
| PS1 | Presenilin 1 |
| PS2 | Presenilin 2 |
| QOL | Quality of Life |
| QOL-AD | Quality of Life – Alzheimer's Disease |
| RUD | Resource Utilisation and caregiver burden |
| SAPK | Stress-Activated Phospho-Kinases |

| | |
|---|---|
| SIB | Severe Impairment Battery |
| t.i.d. | ter in die (Latin), thrice daily |
| TNF-alpha | Tumour Necrosis Factor-alpha |
| US | United States of America |
| VaD | Vascular Dementia |
| WHO | World Health Organisation |
| Wnt | combination of Wg (wingless) and Int (integration genes) |

# 1 Introduction

## *1.1 Aim of this Thesis*

Alzheimer's disease (AD) is an extremely complicated disorder. Although it was described in detail by Alois Alzheimer already more than 100 years ago (see chapter 1.2), the actual cause of the disease still remains elusive. More importantly for the AD patients, there is no cure available and the few medicinal products that are approved for the symptomatic treatment of AD (see chapter 2) are only moderately effective and only for a short period of time (6 to 24 months).

As a result of extensive research, several factors that are considered to play a decisive role in the pathology underlying this devastating disease have been identified. Amongst these are the amyloid-beta peptide, hyperphosphorylated tau protein and inflammatory processes. Despite the extensive research endeavour, only a handful of investigational medicinal products are in late stage of clinical development (see chapter 3.1). More importantly, clinical proof-of-concept is still pending for all of the putatively disease-modifying mechanisms of action. Recently, the two most advanced projects of this category, namely Alzhemed and Flurizan (see chapter 6.1 and 6.2, respectively), failed in Phase III of clinical development due to lack of efficacy.

The aim of this thesis is to analyse whether the lack of success in coming up with an innovative and more effective treatment for AD is due to the lack of understanding of its pathology, a lack of products which could efficiently interact with the proposed pathomechanisms or the lack of clarity on regulatory requirements for obtaining a marketing authorisation. To this purpose chapter 1 and 2 give an overview of what is known to date about AD and the nature and value of the currently available treatment options. Furthermore, the pipeline analysis presented in chapter 3 provides an overview of the drug development activities pursued, especially of the clinical development projects. Additionally, this chapter summarises the results of a comprehensive literature search on the mechanisms of action suspected to play a major role in the underlying pathology of the disease. In chapter 4 the regulatory guidance provided by the EMEA as well as by the FDA is described and discussed. In addition, the regulatory requirements fulfilled by the already approved symptomatic treatment options are analysed in chapter 5 and compared between Europe and the US. Furthermore, chapter 6 summarises the reasons for the discontinuation of the two most advanced clinical development projects, namely Alzhemed and Flurizan. Considering the results of the scientific as well as the regulatory insights, an idealised outline of a clinical development programme is compiled in chapter 7 for a putatively disease-modifying investigational medicinal product. In conclusion, chapter 8 summarises the reasons for the lack of availability of new and effective medicinal products for the treatment of AD.

## *1.2 Historical Background*

Alois Alzheimer was a German psychiatrist and neuropathologist who lived from 1864 to 1915. More than 100 years ago, he gave a seminal presentation to the 37$^{th}$ Meeting of South-West German Psychiatrists in Tübingen. At this meeting he described his results of the post-mortem studies on a 51-year old female patient (Auguste D.) who suffered from progressive pre-senile dementia (Small and Cappai 2006). The ensuing paper published the year after the Tübingen presentation (Alzheimer 1907) was the first thorough description of the typical clinical

characteristics, such as loss of memory and disorientation in time and space, and the neuropathological picture of miliary bodies (amyloid plaques) and dense bundles (neuofibrillary tangles) in an evenly atrophic brain (Blennow et al. 2006). Some years later, Kraepelin, a colleague of Alzheimer's from Munich, named the disease described in the famous paper from 1907 Alzheimer's Disease.

## *1.3 Current Understanding of the Pathology of Alzheimer's Disease*

Alzheimer's disease is an age-dependent neurodegenerative disorder that results in progressive loss of cognitive function associated with severe neuropsychiatric disturbances. It is the most common form of dementia (Jellinger 2006). The disease is characterised by gliosis and tissue atrophy caused mainly by synaptic loss which is most pronounced in the frontal and temporal cortices. Further hallmarks of the disease are extracellular accumulation of the amyloid-beta (A-beta) peptide into amyloid plaques and the intracellular formation of neurofibrillary tangles as a result of abnormal phosphorylation of the microtubule-associated protein tau (Probst et al. 1991).

Familial Alzheimer's disease is a very rare autosomal dominant disease with early onset. It is caused by mutations in the amyloid precursor protein (APP) and presenilin genes which are both linked to the metabolism of beta amyloid. However, the aetiology of the sporadic form of the disease is still unknown (Blennow et al. 2006).

### 1.3.1 Beta Amyloid

The Amyloid Cascade Hypothesis, proposed by Hardy and Allsop in 1991, suggests that the disturbed metabolism of APP is the initiating event in AD pathogenesis. As a consequence of this disturbed metabolism, beta amyloid levels increase and lead to aggregation and plaque formation.

In 1984 Glenner and Wong had already identified beta amyloid (A-beta 42) as the main component of amyloid plaques. Ever since, evidence accumulated that this peptide was indeed the primary neuropathological insult in Alzheimer's disease. For example, the majority of mutations causing familial AD result in increased levels of A-beta 42. Furthermore, individuals with trisomy 21 (Down's syndrome) have three copies of the APP gene and thus a 50% higher level of beta amyloid. All of these patients develop AD within their fourth decade of life (Blennow et al. 2006). Additionally, transgenic mouse models expressing pathogenic mutations of APP and presenilin 1 show increased levels of beta amyloid and amyloid plaques (Hsiao et al. 1996). More importantly, it could be shown that large amounts of soluble A-beta 42 are neurotoxic to cells (Goodman and Mattson, 1994). Presently, research is focussing on soluble, oligomeric and even intracellular A-beta 42 rather than insoluble beta amyloid bound in amyloid plaques, because soluble A-beta 42 levels seem to correlate more strongly with the severity of dementia than the number of existing plaques (McLean et al. 1999).

The following neurotoxicities appear to be triggered by soluble beta amyloid:

| A-BETA 42-MEDIATED NEUROTOXICITY | REFERENCE |
|---|---|
| Disruption of mitochondrial function via binding of the A-beta-binding alcohol dehydrogenase | Lustbader et al. 2004 |
| Induction of apoptotic genes through inhibition of Wnt and insulin signalling | Caricasole et al. 2003<br>Xie et al. 2002 |
| Formation of ion channels triggering loss of calcium homeostasis | Kagan et al. 2002<br>Goodman and Mattson 1994 |
| Stimulation of the JNK/SAPK pathway | Kim et al. 2003 |
| Activation of microglia cells leading to the expression of pro-inflammatory genes, an increase in reactive oxygen species and eventual neuronal toxicity and cell death | Bamberger and Landreth 2001 |

### 1.3.2 Neurofibrillary Tangles

In addition to degenerated neurons and synapses and the deposition of amyloid plaques, another hallmark of AD can be observed microscopically in the brain of AD patients, namely intracellular neurofibrillary tangles. These tangles were shown to be composed of abnormally hyperphosphorylated tau protein (Grundke-Iqbal et al. 1986). Tau is a normal axonal protein that binds to microtubules. Thereby, it promotes microtubule assembly and stability. Tau phosphorylation is regulated by the balance between several kinases, such as GSK-3 beta and CDK5, and phosphatases (Blennow et al. 2006). Hyperphosphorylated tau is no longer able to fulfil its physiological function and causes neurodegeneration by microtubule disruption and a consequent decrease in neurotransmission and axoplasmic transport. Neurons which are able to decrease the level of hyperphosphorylated tau either by degradation of the modified protein or by polymerisation into neurofibrillary tangles survive longer than those without this protective mechanism (Alonso et al. 2008).

The abnormal hyperphosphorylation of tau observed in AD seems to be induced by soluble A-beta 42 which affects GSK-3 beta via its inhibition of the insulin and wnt signalling pathway (Caricasole et al. 2003 and Xie et al. 2002). Although neurofibrillary tangles appear prior to the formation of amyloid plaques (Schönheit et al. 2004), hyperphosphorylation of tau seems to be a consequence of the dysregulation of the APP metabolism which results in increased levels of soluble A-beta 42 and all the consequences described above (Hardy and Selkoe 2002).

### 1.3.3 Inflammation

An increased expression of inflammatory mediators in post-mortem brains of patients suffering from AD has been described in several publications (reviewed by Akiyama et al. 2000). Although epidemiological studies indicate that the use of non-aspirin non-steroidal anti-inflammatory drugs (NSAID) may reduce the risk of developing AD (McGeer et al. 1990, Rogers et al. 1993), the exact role of inflammation in the pathogenesis of AD is still not fully understood. Certain aspects of the immune response, generally summarised as pro-inflammatory processes, are likely to be detrimental and can promote the disease while other aspects, the anti-inflammatory processes including phagocytosis and production of repair and trophic factors,

actually serve to protect against the neurodegenerative properties of amyloid beta (Wyss-Coray 2006).

Microglia are the predominant immune cells which are primarily involved in the inflammatory process in the central nervous system (CNS). It is widely accepted that beta amyloid triggers pro-inflammatory reactions of microglia. Upon stimulation microglia releases cytokines, chemokines and other toxic substances such as tumour necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (Dickson et al. 1993). If the initiating disturbance persists -like beta amyloid in AD- microglia may become chronically activated. Such a continuous release of pro-inflammatory substances results in spread of damage to the surrounding tissue (Schwab and McGeer 2008). Furthermore, the chronically inflammatory milieu in the brain of AD patients seems to impair the anti-inflammatory phagocytic capacity of microglia (Koenigsknecht-Talboo and Landreth, 2005). Thus, activation of microglia towards the anti-inflammatory state may de-escalate the vicious circle of tissue damage due to a chronic inflammatory reaction (Schwab and McGeer 2008).

# 2 Current Treatment

To date there is no cure for AD. Currently available medications appear to be able to produce only moderate symptomatic benefits but do not stop the progression of AD. Approximately 14 different drugs are currently on the market for the treatment of Alzheimer's disease. Most of these (8) are acetylcholine esterase inhibitors. One, memantine, is a NMDA receptor antagonist. However, in clinical practice only four medicinal products are of importance, namely the AChE inhibitors rivastigmine, donepezil and galantamine and the NMDA receptor antagonist memantine (see chapter 2.1 and 2.2).

| MECHANISM OF ACTION | TOTAL PROJECTS |
|---|---|
| Acetylcholine Esterase (AChE) Inhibitors | 8 |
| NMDA Receptor Modulator | 1 |
| Others | 5 |
| **TOTAL** | **14** |

## *2.1 Acetylcholine Esterase Inhibitors*

One of the hallmarks of AD is a deficiency in cholinergic neurotransmission due to the selective loss of cholinergic neurons which leads to memory impairment. This "cholinergic hypothesis" of AD (Francis et al. 1999) became the basis for the current symptomatic treatment approach with Acetylcholine Esterase (AChE) inhibitors (Klafki et al. 2006). The aim is to improve cholinergic function by inhibiting the enzyme (AChE) responsible for the degradation of the neurotransmitter acetylcholine. As a result the concentration of the neurotransmitter in the synaptic cleft is increased and cholinergic transmission is enhanced. Currently, four AChE inhibitors are approved by the European Commission and the FDA. These are tacrine, galantamine, donepezil and rivastigmine.

In 2006, a systematic review of the available randomised, double-blind, placebo-controlled clinical trials of AChE inhibitors was conducted by the Cochrane

Collaboration[1]. It supported the use of three of the approved AChE inhibitors, namely rivastigmine, donepezil and galantamine for the treatment of mild to moderate AD. The treatment effects observed after six months were only moderate and of similar size for the three substances (Birks 2006). Tacrine, the first centrally acting AChE inhibitor approved by the FDA for the treatment of AD in 1993, was not included in the analysis by the Cochrane Collaboration due to its obvious disadvantages compared to the other AChE inhibitors. These are poor oral bioavailability, short half-life requiring four times daily dosing and hepatotoxic side-effects in approximately 50% of the patients (Madden et al. 1995, Watkins et al. 1994).

Although AChE inhibitors can slow down the mental decline associated with AD only for a short time, this seems to be sufficient to delay the need to go to a nursing home for up to 22 months in some patients (Bren 2003). Considering the enormous socio-economic burden associated with the care required by the steadily growing number of AD patients, delaying the cost-intensive final phase of the disease by several months seems to justify the use of AChE inhibitors despite their only moderate symptomatic benefits.

## *2.2 NMDA Receptor Antagonists*

N-methyl-D-aspartate (NMDA) receptors are a sub-group of the ionotropic glutamate receptors which are ligand-gated ion channels. Glutamate represents the main excitatory neurotransmitter in the CNS and a physiological level of glutamate-receptor activity is essential for normal brain function (Kornhuber and Weller 1997). In AD, excessive activation of the NMDA receptor due to glutamate excitotoxicity, is believed to cause increased intracellular $Ca^{2+}$ levels which in turn trigger downstream events that ultimately lead to neurodegeneration (Hynd et al. 2004).

While potent NMDA receptor antagonists like MK-801 produce psychotomimetic side effects such as delusions and hallucinations, memantine is a non-competitive NMDA receptor antagonist with only moderate affinity (Kornhuber et al. 1989). Based on the only moderate affinity, memantine seems to be able to protect neurons from glutamate-mediated excitotoxicity without affecting the physiological NMDA receptor activation (Sonkusare et al. 2005). Thereby, cognitive function is improved and functional decline is, at least for a short time, slowed down in patients with moderate to severe AD (Klafki et al. 2006).

[1] The Cochrane Collaboration is an independent, international non-profit organization, which was founded in 1993 and named after the British epidemiologist, Archie Cochrane. It produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions.

# 3 New Treatment Approaches in Development

As the currently available medicinal products for the treatment of AD are purely symptomatic and only of moderate efficacy (see chapter 2), there is an enormous medical need for new therapeutic interventions which target the presumed underlying pathogenic mechanisms of the disease.

## *3.1 Actual Pipeline Overview*

Currently, there are 226 projects in active development for Alzheimer's disease which are registered in the Investigational Drug database (IDdb3). As it is sometimes difficult to judge whether a development project is actively pursued by the company, only such projects are included in this number for which any relevant news were published after December 2004. This cut-off date was arbitrarily set and is assumed to provide a reasonable time-frame in which development results for an actively pursued development project might have been expected. An overview of all these 226 projects is given in the attachment (see Annex 10.1).

46 of the projects considered for this analysis are drug discovery programmes where a lead candidate has not yet been identified for preclinical development. These drug discovery programmes can be grouped into 4 main classes according to their mechanism of action or target.

| MECHANISM OF ACTION | TOTAL PROJECTS |
|---|---|
| Amyloid Synthesis Inhibitors: | |
| Unspecified or Mixed Targets | 4 |
| Beta secretase/BACE inhibitors | 16 |
| Gamma secretase inhibitors | 5 |
| Nicotinic Acetylcholine Receptor (nAChR) agonists | 3 |
| Muscarinic Receptor Modulators | 3 |
| Others | 15 |
| **TOTAL** | **46** |

83 projects are in active clinical development. 54% of all projects are in preclinical development (97 out of 180). The compounds can be grouped into 12 classes according to their different mechanisms of action, as shown in the table below.

| MECHANISM OF ACTION | TOTAL PROJECTS | PROJECTS 2006 | | | | |
|---|---|---|---|---|---|---|
| | | Pre-clinic | Phase I | Phase II | Phase III | Prereg. & Registered |
| Amyloid Synthesis Inhibitors | | | | | | |
| Unspecified | 6 | 5 | 1 | 0 | 0 | 0 |
| Beta Secretase/BACE Inhibitors | 4 | 3 | 1 | 0 | 0 | 0 |
| Gamma Secretase Inhibitors | 12 | 3 | 7 | 1 | 1 | 0 |
| Beta Amyloid Aggregation and/or Deposition Inhibitors | 28 | 19 | 3 | 5 | 1 | 0 |
| Chelating Agents | 6 | 4 | 0 | 1 | 1 | 0 |
| Acetylcholine Esterase (AChE) Modulators | 16 | 7 | 4 | 2 | 2 | 1 |
| Nicotinic Acetylcholine Receptor (nAChR) Agonists | 8 | 2 | 2 | 4 | 0 | 0 |
| Muscarinic Receptor Modulator | 4 | 1 | 1 | 2 | 0 | 0 |
| NMDA Receptor Modulator | 3 | 2 | 0 | 1 | 0 | 0 |
| 5HT Receptor Modulator | 11 | 5 | 3 | 3 | 0 | 0 |
| Ion Channel Modulators | 3 | 2 | 0 | 1 | 0 | 0 |
| Phosphoric Diester Hydrolase (PDE) 4 Inhibitors | 5 | 2 | 2 | 1 | 0 | 0 |
| Vaccines | 15 | 9 | 3 | 3 | 0 | 0 |
| Others | 59 | 33 | 12 | 11 | 3 | 0 |
| **TOTAL** | **180** | **97** | **39** | **35** | **8** | **1** |

### *Conclusion*

The category “Others” comprises mechanisms of actions which are pursued only by one or two companies. Analysis of the database revealed that within drug discovery as well as in development programmes approximately one third of the projects cannot be assigned to a certain mechanism of action. This reflects the complexity of AD and shows that a great number of unvalidated targets are studied in the course of identifying the relevant pathogenic processes underlying the disease.

On the other hand, the numbers of the pipeline analysis also show that the main target in AD research still is amyloid beta, either its synthesis or its deposition and aggregation. Vaccines can actually also be included in this group as most of them target amyloid beta. Another focus is on a second generation symptomatic treatment via modulation of nAChR or 5HT receptors (see chapter 3.3).

## *3.2 Rationale for the Various Mechanisms Examined for the Treatment of Alzheimer's Disease*

The rather complex pathophysiology of AD is not yet fully understood and it appears likely that the disease has more than one cause. Consequently, research aiming at the identification of disease modifying therapies is focussing on several main symptoms, such as A-beta plaques, neurofibrillary tangles, and inflammatory processes. Furthermore, it is generally accepted that the increase of acetylcholine levels in the synaptic cleft may improve the symptoms of AD. Thus, several of the examined mechanisms aim at stabilisation or increase of acetylcholine levels.

### 3.2.1 Amyloid Synthesis Inhibitors

As discussed above (see chapter 1.3.1, Hardy and Allsop 1991) the most widely accepted hypothesis to explain the mechanism leading to AD is the amyloid cascade hypothesis. Accordingly, beta amyloid plays a central role in the pathogenesis. It is produced proteolytically from APP by sequential cleavage of the so-called beta- and gamma-secretases.

#### *Beta-Secretase / BACE Inhibitors*

The majority of APP is processed through alpha-secretase in a non-amyloidogenic pathway that produces a soluble version of APP and an 83-amino acid residue C-terminal fragment (Esch et al. 1990). Only a small portion of APP undergoes cleavage by BACE-1 (beta-site amyloid precursor protein-cleaving enzyme) in an amyloidogenic pathway. However, the generation of beta amyloid is not the result of abnormal or pathological APP processing. On the contrary, beta amyloid is secreted constitutively by cells in culture and can be detected in plasma and CSF of healthy humans (Haass et al, Seubert et al. 1992). Nevertheless, when BACE-1 was inactivated in mice, these knock-out animals hardly produce any beta amyloid. Furthermore, they did not develop a severe phenotype (Luo et al. 2001). Thus, targeting BACE-1 may be a particularly promising therapeutic approach and has been a major focus of drug discovery efforts ever since its discovery and cloning in 1999 (Sinha et al. 1999).

Despite these promising preconditions the identification of specific small molecule inhibitors suitable for drug development seems to be rather difficult (Citron 2004). This is also confirmed by the pipeline analysis (see Annex 10.1). To date there are about 16 drug discovery programmes and most of the major pharmaceutical companies are active in this field. Nevertheless, only one project has reached Phase I of clinical development (CTS-21166, Zapaq/Astellas). Clinical proof of concept still needs to be obtained.

#### *Gamma-Secretase*

The 83-amino acid long C-terminal cleavage product generated by alpha-secretase and the 99-amino acid long C-terminal fragment generated by BACE-1 are substrates for gamma-secretase. Its activity leads to the production of 40- and 42-amino acid long beta amyloid, the latter being more prone to aggregation. However, in healthy humans A-beta 42 makes up only 5% of the amyloid beta produced (Suzuki et al. 1994).

Gamma-secretase is a high molecular weight protein complex consisting of several components, namely of the presenilins (PS1 and PS2), nicastrin, anterior pharynx defective-1 (Aph-1) and the presenilin enhancer-2 (Pen-2). PS1 and PS2 constitute the catalytic domain of the enzyme. Gamma-secretase is involved in the processing

of multiple substrates, most importantly N-cadherin and notch (reviewed by De Strooper 2003). Notch signalling regulates many aspects of metazoan development and tissue renewal. The misregulation or loss of Notch signalling underlies a wide range of human disorders, from developmental syndromes to adult-onset diseases and cancer (Kopan and Ilagan 2009). Thus, even specific gamma-secretase inhibitors may induce mechanism-based toxicities due to their indirect influence on the notch signalling pathway. Consequently, drug discovery efforts were focussed on second generation gamma-secretase inhibitors which do not affect notch signalling. Eli Lilly's semagacestat is one example and two big Phase III clinical studies have been started in 2008.

### 3.2.2 Amyloid Aggregation Inhibitors

This approach is also based on the amyloid cascade hypothesis (see chapter 1.3.1). A wealth of projects is targeting the prevention of A-beta 42 aggregation or deposition (see Annex 10.1). This mechanism is mainly based on two aspects of AD pathology. Firstly, plaques seem to be a kind of reservoir of beta amyloid which can diffuse and cause tau pathology over the course of many years (reviewed by Bloom et al. 2005). Secondly, aggregated A-beta 42 is a potent stimulator of microglia and the subsequent chronic inflammatory reactions (see chapter 1.3.3).

Most projects in this category are based on antibody technology. But there are also some small molecules in development such as AZD-103 (Transition/Elan) which has entered Phase II trials. Furthermore, chelating agents are also targeting beta amyloid aggregation, although by different means (see 3.3.3). Due to the neurotoxicity of soluble/oligomeric A-beta 42 (see chapter 1.3.1) it may, however, not be sufficient to prevent plaque formation without facilitating beta amyloid clearance.

### 3.2.3 Chelating Agents

This treatment approach is based on the observation that amyloid beta aggregation is, at least partially, dependent on the metal ions $Cu^{2+}$ and $Zn^{2+}$. A-beta 42 can be precipitated by zinc and is radicalised by copper. Furthermore, both metals are markedly accumulated in plaques (Bush 2008). Thus, compounds like the antibiotic clioquinol, which is a known $Cu^{2+}/Zn^{2+}$ chelator, promote solubility of A-beta 42 and prevent plaque formation. Two projects are in Phase II of clinical development (compare Annex 10.1). However, as mentioned above (3.3.2) due to the neurotoxicity of soluble/oligomeric A-beta 42 (see chapter 1.3.1) it may not be sufficient to prevent plaque formation without facilitating beta amyloid clearance.

### 3.2.4 Nicotinic Acetylcholine Receptor Agonists

As discussed in chapter 2.1, one of the hallmarks of AD is a deficiency in cholinergic neurotransmission due to the selective loss of cholinergic neurons. This cholinergic deficit is also associated with the loss of nAChRs (Engidawork et al. 2001). As cognitive performance has been linked to nAChR function in the hippocampus (Buccafusco et al. 2005), stimulation of these receptors via selective nAChR agonists may improve cognitive deficits observed in AD patients. Furthermore, nAChRs play an important role in neuroprotection against beta amyloid-induced cytotoxicity (Mudo et al. 2007), and thus, nAChR agonists may even counter the loss of synapses and neurons.

Several projects have entered Phase II of clinical development (see Annex 10.1) and hopefully proof-of-concept for this mechanism may soon be available.

### 3.2.5 Muscarinic Receptor Modulators

As discussed above (see chapter 3.3.1), the majority of APP is processed through alpha-secretase in a non-amyloidogenic pathway. This non-amyloidogenic cleavage can be stimulated by muscarinic receptor agonists and results, at least in tissue culture, in a reduction in beta amyloid levels (Wolf et al. 1995). Therefore, muscarinic receptor agonists were suggested to be potentially useful not only for symptomatic treatment of AD but might even influence the course of the disease (Fisher 2000).

As two projects have entered Phase II of clinical development (see Annex 10.1) proof-of-concept may soon be available.

### 3.2.6 5-HT (Serotonin) Receptor Modulators

The loss of monoaminergic neurons, such as serotonergic neurons, leads not only to cognitive decline but also to behavioural symptoms like anxiety, insomnia and depression (Schmitt et al. 2006). However, the action of 5-HT (serotonin) are mediated through seven major receptor classes (5-$HT_{1-7}$), which to date comprise a total of 14 distinct mammalian receptor subtypes (Baez et al. 1995). Thus, it is not yet fully understood, which receptor subtype needs to be modulated in which way (inhibition or stimulation) to positively influence the cognitive and/or behavioural symptoms observed in AD patients.

Recent publications seem to support a role of the 5-$HT_4$ receptor in the treatment of AD. It is believed that agonists of this receptor subtype stimulate the release of acetylcholine, improve memory and learning and regulate the metabolism of APP (Robert and Lezoualch 2008). Furthermore, the 5-$HT_6$ receptor has been implicated in AD. This receptor subtype is localized almost exclusively in the CNS, predominating in brain regions associated with cognition and behaviour. Although its function is still not completely understood, it seems to be involved in the regulation of putatively cholinergic-mediated behaviours, anxiety and memory performance (reviewed by Upton et al. 2008).

This current understanding of the role of 5-HT receptors in AD is also reflected in the pipeline (see Annex 10.1). Half of the projects under investigation are 5-$HT_6$ receptor antagonists, two of these have reached Phase II of clinical development and may soon provide proof-of-concept in man. Two projects are 5-$HT_4$ receptor agonists, one is in Phase I and the other in Phase II of clinical development.

### 3.2.7 Ion Channel Modulators

Besides the amyloid cascade hypothesis (see chapter 1.3.1) and the involvement of hyperphosphorylated tau protein (see chapter 1.3.2) another hypothesis proposes that the dysregulation of calcium homeostasis may be a key factor accelerating some pathological processes in AD (reviewed by Bojarski et al. 2008). Accordingly, the underlying biochemical events leading to neuronal death appear to be activation of calcium channels, disruption of intracellular calcium stores and subsequent production of free radicals by calcium-sensitive enzymes (Hölscher 1998). The critical role of calcium signalling is supported by two facts. Firstly, presenilins, which are mutated in some patients with familial AD, were shown to form low conductance calcium channels in the endoplasmatic reticulum (Tu et al. 2006). In turn, the elevated cytosolic calcium concentration caused by the mutation facilitates beta amyloid generation (reviewed by Bojarski et al. 2008). Secondly, the molecular mechanism of memantine (see chapter 2.2) as an uncompetitive, low-affinity, open-channel (NMDA receptor) blocker further points towards the involvement of calcium.

memantine prevents excessive calcium influx through the NMDA receptor-associated ion channel and thus protects cells from glutamate-mediated excitotoxicity and subsequent cell death (Lipton 2005).

However, to avoid -especially cardio-vascular- side-effects, brain-selective ion channel modulators are required. This seems to be quite a challenge which is also reflected by the low number of projects in this category (see Annex 10.1).

### 3.2.8 Phosphodiesterase (PDE) 4 Inhibitors

Cyclic adenosine monophosphate (cAMP) is a second messenger that plays an important role in biochemical processes regulating cognition and memory consolidation (Isiegas et al. 2008). Prolongation of cAMP signalling via phosphodiesterase inhibitors, especially PDE-4 inhibitors, seems to have positive effects on learning and memory. Preclinical studies indicated that PDE-4 inhibitors can counteract deficits in long-term memory caused by over-expression of mutant forms of human APP. Furthermore, PDE-4 inhibitors are known to have neuro-protective, neuro-regenerative as well as anti-inflammatory effects (Ghavami et al. 2006). Based on the fact that AD is characterised not only by cognitive impairment but is also now recognised as having a neuro-inflammatory component, targeting PDE-4 with selective inhibitors may offer a novel therapeutic approach for slowing the progression of the disease.

### 3.2.9 Vaccines

The principle of amyloid beta vaccination was first reported in 1999 (Schenk et al. 1999). AD transgenic mice were actively immunised with fibrillar amyloid beta. Subsequently, it could be shown that amyloid beta deposition was attenuated. Comparable results were obtained using a passive immunisation approach with antibodies against amyloid beta (Bard et al. 2000). The following, presumably not mutually exclusive mechanisms, have been proposed to explain the above findings:

- Antibodies bound to amyloid plaques trigger amyloid beta clearance by microglia (Schenk et al. 1999).
- Circulating antibodies bind soluble amyloid beta in the periphery and thereby cause an amyloid beta efflux from the brain (DeMattos et al. 2001). This mechanism is also known as the so-called “peripheral sink hypothesis”.

However, the first clinical development programm of an active AD vaccine (AN-1792 from Elan/Wyeth) failed in Phase IIa due to aseptic meningoencephalitis in 6% of the patients treated (press release of the two companies on January 18, 2002). Autopsy studies demonstrated a T-cell-mediated autoimmune response. Nevertheless, proof-of-concept could be obtained in some of the antibody responders, who showed positive trends in several efficacy measures (Nicoll et al. 2003).

Several attempts have been made to develop active as well as passive immunisation strategies against AD (see Annex 10.1). Some of the monoclonal antibodies used for passive immunisation, like solanezumab (Eli Lilly), PF-4360365 (Pfizer) and bapineuzumab (Elan/Wyeth), are listed under the category “beta amyloid deposition/aggregation inhibitors”. The former two are in Phase II and bapineuzumab is in Phase III of clinical development. However, the efficacy of this mechanism has not yet been established.

# 4 Regulatory Requirements for the Clinical Development of Medicinal Products for the Treatment of Alzheimer's Disease

## *4.1 EMEA*

### 4.1.1 CPMP/EWP/553/95 – Guideline on Medicinal Products in the Treatment of Alzheimer's Disease

Until the beginning of this year clinical development programmes for new therapies for the treatment of AD needed to consider the EMEA "Guideline on Medicinal Products for the Treatment of Alzheimer's Disease" (CPMP/EWP/553/95). This guideline was initiated already in 1992 but did not come into operation before January 1998.

The guideline defines the term "dementia" based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-III revised 1988, and IV) and the International Classification of Disease (ICD) 10 of the World Health Organisation (WHO), as a syndrome characterised by dysmnesia, intellectual deterioration, changes in personality and behavioural abnormalities. Although there are many different forms of dementia such as vascular dementia, dementia with Parkinson's Disease and with Lewy Bodies, fronto-temporal dementia and others, this guideline focuses on AD as the most common form of dementia. It mentions that medicinal products in development should either address symptomatic change or modification of the aetiological and pathophysiological processes but does not provide any further guidance on the latter aspect. Disease modification is neither further specified nor are any regulatory requirements detailed for such an approach. To the contrary, the guideline states explicitly that it concentrates on the assessment of symptomatic improvement.

The guideline provides some information on the diagnosis of AD, the assessment of efficacy and on the general strategy of the clinical development programme.

***Diagnosis***

The diagnosis of AD is a two-step procedure where in the first step the clinical diagnosis of dementia is made based on a history of a steadily progressive course and in the second step any other causes of dementia are excluded. To document cognitive dysfunction the Mini Mental State Examination (MMSE)[2] is recommended. The degree and the severity of AD, classified as mild, moderate or severe, should be determined by using specific or global rating instruments which are not further discussed in the guideline.

***Assessment of Therapeutic Efficacy***

Generally, treatment of AD could target symptomatic improvement, slowing or arrest of disease progression or primary prevention at a pre-symptomatic stage. Concerning the symptomatic improvement on which this guideline focuses, mainly the three following domains are of importance:

[2] Multi-item instrument examining orientation, registration, attention, calculation, recall, visospatial abilities and language. Maximum score is 30. In general, scores fall into four categories: 24–30: "normal" range; 20–23: mild cognitive impairment or possible mild AD; 10–19: moderate AD; 0–9: severe AD.

- Cognition (cognitive endpoint)
  The ADAS-cog[3] is recommended.
- Activities of daily living (functional endpoint, e.g. ADCS-ADL[4])
  Several scales to assess the activities of daily living (physical as well as instrumental) were proposed but none is specifically recommended in the guideline.
- Overall clinical response (global endpoint)
  Subjective independent rating of the patient's condition by a clinician experienced in the management of AD patients. No instrument is recommended.

In mild to moderate AD, efficacy should be demonstrated via two primary endpoints, namely one cognitive endpoint and ideally a functional endpoint. In more advanced forms where cognitive improvement is no longer feasible, statistically significant improvement on the functional and global domain may be considered to demonstrate efficacy.

The guideline recommends a run-in period to wash out the effect of previously administered medicinal products and to be able to determine for each patient the baseline values of the measurement tools used in the trial. If a claim for improvement of behavioural symptoms is aimed at, specific trials need to be designed with behavioural symptoms as primary endpoint.

***General Strategy***

Most of the recommendations provided in this part of the guideline are rather generic and apply to clinical development programmes for any indication. Namely, Phase I should establish the pharmacological rationale for the efficacy and must define absorption, distribution, metabolism and elimination of the drug. Phase II should show preliminary efficacy, assess short-term adverse reactions, determine the drug's pharmacokinetic characteristics and provide information on the future therapeutic as well as the maximum tolerated dose. Phase III finally should demonstrate efficacy, indicate the duration of the therapeutic effect and assess the medium and long-term adverse effects.

The only AD-specific recommendations given are that clinical trials should be conducted in patients suffering from mild to moderate AD. Furthermore, trials aiming at showing short-term improvement should last at least 6 months but studies of one year are recommended to demonstrate maintenance of efficacy. Additional 12 months open label follow-up of at least 100 patients is recommended to demonstrate long-term safety. More importantly, concomitant treatments which may impair alertness, intellectual function and behaviour should be avoided, i.e. hypnotics, anxiolytics, antidepressants, antipsychotics, anti-cholinergics and memory enhancers. Lastly, interaction studies between the investigational drug and drugs commonly used in the elderly should be conducted.

As the course of the disease and thus the evaluation of the efficacy may differ within subgroups of patients with AD, prognostic factors such as Apo lipoprotein E genotype, Lewy body pathology, severity of dementia and vascular risk factors should be taken into account when the drug's efficacy is analysed.

[3] ADAS-cog maximum score is 70. The higher the score, the poorer the performance.
[4] ADCS-ADL consists of 45 items, maximum score is 30. 24-30 normal, depending on age, education, complaints; 20-23 mild AD; 10-19 moderate AD; 1-9 severe AD; 0 profound AD.

### 4.1.2 The Revised Guidance on Medicinal Products in the Treatment of Alzheimer's Disease

Although AD is the most common form of dementia, the dementia syndrome comprises several subtypes such as vascular dementia, dementia associated with Parkinson's and Lewy Body Disease, fronto-temporal dementia and others. As the current guideline mainly deals with AD, a revision was initiated in 2007. Furthermore, significant progress has been made in basic as well as clinical research and many of the new treatment approaches investigated (see chapter 3.1 and Annex 10.1) target aetiological and pathophysiological processes. However, no guidance was provided for these approaches in the original guideline. The revised "Guideline on Medicinal Products for the Treatment of Alzheimer's Disease and Other Dementias" (CPMP/EWP/553/95 Rev.1) addresses both aspects. It was adopted in July 2008 and has come into effect as of February 2009.

The table below gives an overview of the main differences between the original and the revised guideline. Only topics are listed which were affected by the revision of the guideline.

***Comparison of the Main Revisions***

| TOPIC | ORIGINAL GUIDELINE | REVISED GUIDELINE |
|---|---|---|
| Indication | Focus on AD | AD and other dementias, like<br>• vascular dementia (VaD)<br>• mixed forms of AD and VaD<br>• Parkinson's Disease (PD)<br>• Lewy-Body Disease (LBD)<br>• Huntington's Disease<br>• Fronto-temporal dementia |
| Legal Basis | Not defined | Directive 2001/83/EC as amended in conjunction with all relevant CHMP guidelines. Especially a reference is made to the **ICH E7** guideline, specifying the geriatric requirements. |
| Diagnosis | Two-step-procedure:<br>• clinical diagnosis (progressive deterioration of cognitive and non-cognitive functions, some behavioural and functional consequences)<br>• exclusion of any other causes of dementia<br>Recommendation of the MMSE to define the severity of the dementia. | Three-step-procedure:<br>• clinical diagnosis and<br>• exclusion of any other causes of dementia as defined in the original guideline<br>• diagnostic classification of the dementia sub-type (via brain imaging techniques and laboratory methods)<br>Recommendation of the MMSE to define the severity of the dementia. |

| | | |
|---|---|---|
| Disease-Modification | No guidance given, focus on assessment of symptomatic improvement. | Regulatory requirements for disease-modification:<br>• Delay of the underlying pathological or pathophysiological process **and**<br>• Improvement of clinical signs and symptoms of dementia<br>Due to lack of validated biomarkers, a two step procedure is recommended:<br>• Delay in the natural course of progression based on clinical signs and symptoms<br>Claim: Delay of disability<br>• Biological and/or neuroimaging data showing delay in e.g. brain atrophy<br>Full claim: Disease-modification |
| Therapeutic Efficacy | Placebo-controlled trials | Symptomatic treatment with AChE-inhibitors is regarded as standard of care. Therefore,<br>• Long-term placebo-controlled trials are ethically no longer justifiable<br>• add-on-designs are recommended<br>• active control parallel group trials required for symptomatic endpoints<br>• three-arm studies (placebo, investigational drug, active control) are recommended |
| Measurement Tools | Cognitive endpoint: ADAS-cog<br>Functional endpoint: ADL<br>Global endpoint: CDR[5]<br>Quality of Life: Due to lack of validation no recommendation made | Cognitive endpoint: ADAS-cog<br>Functional endpoint: ADL, IADL, DAD, ADCS-ADL<br>Global endpoint: CDR, ADCS-CGI-C[6], CIBIC-plus[7]<br>Quality of Life: Due to lack of validation no recommendation made but ADRQL and QOL-AD are named for AD. Furthermore, BEHAVE-AD and BRSD are mentioned to assess behavioural |

[5] Six categories are tested: memory, orientation, judgement, commununity affairs, home and hobbies, and personal care. A five point scale is used to rate each category: 0 is normal, 0.5 is questionable impairment , 1 is mild impairment, 2 is moderate impairment, and 3 is severe impairment.

[6] The format is similar to CIBIC-plus (see next footnote) but the clinician is not blinded. It evaluates the global change from baseline, using the following scores: 1=marked improvement; 2=moderate improvement; 3=minimal improvement; 4=no change; 5=minimal worsening; 6=moderate worsening; 7=marked worsening.

[7] The format consists of the assessment by an independent clinician, blinded to the results of the study, based on observation of the patient at an interview and information provided by the caregiver. Rating scale from 1 to 7 with 1=markedly improved, 4=no change and 7=markedly worse.

| | | |
|---|---|---|
| | | symptoms. |

| | | |
|---|---|---|
| General Strategy | Phase I: Pharmacological rationale and standard pharmacokinetics | Phase I: In addition to pharmacological rationale and ADME, pharmacokinetic and –dynamic interactions with other anti-dementia drugs are recommended as well as studies in hepatic and/or renal impaired patients<br><br>Phase III: No ideal study design to show disease-modifying effects can be recommended.<br><br>• To show a slowing of disease progression long-term placebo-controlled trials are needed<br>• 18 months seems to be the minimal duration of confirmatory trials to show clinical improvement<br>• traditional slope analysis (rate of change over time) may be misleading. Therefore, two time points should be defined at which the study endpoints are assessed<br>• studies can be enhanced by randomised delayed start or randomised withdrawal<br>• disease milestones may be analysed by comparing time to milestone<br>• a full claim of “disease modification” may be obtained through a suitable study design, an accepted novel analysis or a validated biomarker.<br><br>Additional prognostic factors to be considered:<br><br>• Amyloid beta and tau protein in the CSF<br>• Neuroimaging parameters |

| | | |
|---|---|---|
| General Strategy (continued) | Safety evaluation: According to guideline on ”Clinical Investigation of Medicinal Products for Long-Term Use” from 1987 (EudraLex Vol. 3CC6a) at least 100 patients followed for one year. | Safety evaluation: According to ICH E1 which provides guidance for the safety assessment of a compound intended for long-term use.<br>• 300-600 patients should be treated for 6 months at dosage levels intended for clinical use and at least 100 of these should be exposed for a minimum of one-year to the investigational drug.<br>• A total number of 500 to 1.500 individuals should be treated with the compound during the development phase.<br>Neurological, psychiatric and cardiovascular adverse events should be evaluated in particular during the safety assessment. |

***Conclusion***

The revised guideline concentrates more on diagnostic criteria than the original guideline because it is recommended to start clinical trials with a study population which is as homogenous as possible. Therefore, the importance to classify the sub-type of dementia is stressed. This procedure has implications on defining the inclusion and exclusion criteria for clinical trials. Furthermore, many new assessment tools are available. Although most of them are not finally validated, they are useful to determine primary and secondary endpoints in clinical studies.

Disease-modification is covered for the first time. However, as there is still a lack of agreement on the methods for demonstrating disease-modification, the guideline does not offer specific recommendations. A break-through may be expected as soon as biomarkers as surrogate endpoints will be sufficiently qualified and validated.

### 4.1.3 Paediatric Investigation Plan (PIP) Waiver

According to Article 11 of the Paediatric Regulation (Regulation (EC) No 1901/2006) the requirement to submit a paediatric investigation plan (PIP) shall be waived for specific medicinal products or classes of medicinal products that:

- are likely to be ineffective or unsafe in part or all of the paediatric population,
- are intended for conditions that occur only in adult populations,
- do not represent a significant therapeutic benefit over existing treatments for paediatric patients.

In accordance with Article 14 of the Paediatric Regulation, the Paediatric Committee has adopted a list of conditions that occur only in adult populations. All classes of medicinal products intended to treat these conditions will therefore be exempt from the requirement for a paediatric investigation plan.

In respect of AD, the consolidated EMEA decision on the list of class waivers, adopted on 14 July 2008 (EMEA/360425/2008 P/47/2008) states that “Alzheimer’s disease rarely occurs before the age of 50 years and average age of onset is around the age of 65. Although Familial Alzheimer’s Disease occurs earlier in life, it has been reported to occur only as early as the age of 30”. Thus the requirement to submit a PIP for any medicinal product intended for the treatment of AD may be waived on the grounds that AD is a conditions that occurs only in the adult population.

However, in view of the submission of an application for Marketing Authorisation (MA) it may be advisable to request confirmation of whether the scope of the EMEA decision on a class waiver for a condition is applicable to the investigational product in development. Such a confirmation may facilitate the future validation of a subsequent application for MA and can be obtained by submitting the corresponding template provided by the EMEA.

### 4.1.4 Geriatric Requirements

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) finalised the guideline E7 “Studies in support of special populations: geriatrics” in June 1993. In Europe the ICH E7 guideline was adopted in September of the same year and became operational in March 1994 (CPMP/ICH/379/95).

Generally, medicinal products should be studied in all relevant age groups but primarily in those that are representative of the population that will later be treated by the drug. According to the ICH E7 guideline, the geriatric population is arbitrarily defined as comprising patients aged 65 years of age and older. This population can be further sub-divided into two groups, whereas the 65 to 75 years old patients form the group of “elderly patients” and the ones older than 75 years form the group of “very elderly patients”.

Most of the known differences between younger and older patients are of a pharmacokinetic nature, mainly due to renal and/or hepatic impairment. Although the occurrence of abnormal renal and/or hepatic function becomes more likely the older a patient is, this condition can also occur in younger patients. As it is important to study the influence of impaired excretory function on the pharmacokinetics of the compound, this should be studied either in younger patients with renal/hepatic impairment or in the elderly.

Furthermore, it is stressed in the ICH E7 guideline that drug-drug interactions are particularly important to geriatric patients as they have a higher incidence of concomitant diseases (multi-morbidity) and thus may have to take several different medicinal products at the same time. Although the kind of drug-drug interaction studies needs to be defined on a case-by-case basis, it is recommended to study interaction with digoxin and oral anticoagulants, because they are widely used in the elderly. Furthermore, drugs with extensive hepatic metabolism should be studied together with hepatic enzyme inducers like phenobarbital and inhibitors such as cimetidine. Additionally, interaction studies with cytochrome P-450 inhibitors should be conducted if the drug is metabolised by this enzyme system. Generally, drug-drug interactions should be investigated with all other drugs that are likely to be used together with the test compound.

## *4.2 FDA*

### 4.2.1 Availability of Guidelines

The FDA provides only a draft guideline "Guidelines for the Clinical Evaluation of Antidementia Drugs" from November 1990 for the development of new therapies for AD. According to the Division of Drug Information, Center for Drug Evaluation and Research of the FDA this draft guideline was never finalised.

Although there are many different forms of dementia (see chapter 4.1.1) the draft guideline of the FDA intends primarily to provide advice on the development of new treatments for patients suffering from AD. It defines the term "dementia" based on the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-III revised 1988) and the National Institute of Neurological Disorders and Stroke (NINDS)[8] and Alzheimer's Disease and Related Disorders Association (ADRDA) as a progressive, irreversible decline in intellectual and cognitive abilities.

As the draft guideline dates back to 1990, it is not surprising that no particular guidance is provided for disease-modifying treatment approaches. However, the distinction made between symptomatic and definitive/disease-modifying treatments is mentioned. But it is also pointed out that until the aetiology and/or pathogenesis of the underlying processes is fully understood, it may not be expected that disease-modifying treatments will be developed. Thus the draft guideline focuses on advice for the development of symptomatic treatments targeting the "core" phenomena of AD, namely the disability to learn new things and retrieve information from the short- to mid-term memory.

Despite the above-mentioned focus on AD and symptomatic treatment the draft guideline provides surprisingly few specific recommendations for the development of an anti-dementia drug. It mainly explains general aspects and regulatory requirements of clinical drug development such as compliance with the Code of Federal Regulations (CFR), advice on filing an Investigational New Drug (IND) application or what the scope of the different clinical development phases is and the importance of obtaining scientific advice from the FDA

In the following a summary of the AD-specific guidance of the draft guideline is given:

***Diagnosis***

The FDA recommends defining a diagnosis of AD as a progressive, irreversible decline in intellectual and cognitive abilities based on the DSM-IIIR and the NINDS/ADRDA criteria. Additionally, other types of dementia should be excluded. The severity and stage of AD must be characterised by some instrument with clinically understandable endpoints and reasonable degree of acceptance within the community of experts, like the Reisberger's Global Deterioration Scale[9]. Furthermore, an assessment tool must be applied which rates the performance of each patient on some objective comprehensive test of cognitive function, like MMSE, ADAS, DRS or others.

[8] The NINDS conducts and supports research on brain and nervous system disorders. Created by the US government in 1950, it is one of the more than two dozen research institutes and centers that comprise the National Institutes of Health (NIH).

[9] Instrument to assess the magnitude of cognitive, functional and behavioural decline with 7 stages of cognitive decline. 1=no cognitive decline, 2=very mild, 3=mild, 4=moderate, 5=moderately severe, 6=severe and 7=very severe.

However, as a standard system to stage the severity of AD has not yet been adopted, the FDA does not recommend the use of specific instruments to ensure a sound diagnosis of AD.

***Assessment of Therapeutic Efficacy***

To establish efficacy, the sponsor must provide clinically significant effects on the "core" phenomena of AD, namely the disability to learn new things and retrieve information from the short- to mid-term memory. To achieve this, more than one positive controlled clinical trial is required and the trials need to show superiority to control (placebo) on a global assessment performed by a skilled clinician and an objective test on cognitive function. Thus, two primary endpoints must show statistical significance. Although the FDA points out in the draft guideline that a placebo is the preferred choice for an internal control in clinical studies evaluating new anti-dementia treatments, the Agency also concedes that long-term placebo-controlled clinical trials may only be acceptable as long as no effective treatment is available. Otherwise, any test compound needs to be able to show efficacy on top of the standard of care treatment.

No recommendation on the choice of measurement instruments is given. The Agency states the choice of instrument not to be important as long as a performance-based assessment was provided. The sponsor needs to show that the chosen instrument has been clinically validated, like the MMSE, ADAS, DRS and others. Some recommendations are given on the practical performance of the global assessment to avoid bias or inter-examiner variability.

***General Strategy***

The draft guideline puts great emphasis on the need to protect the study participants from potential risks of the new treatment. Thus, an ideal experimental setting for the initial Phase II studies would be within a medically supervised environment such as a hospital or a nursing home. However, to move an ambulatory demented patient into a medically supervised environment for the sole purpose of participating in a study is considered to be an unacceptable hardship for the patient. Thus, the Agency recommends the following alternative experimental conditions for the initial Phase II studies:

1. Ambulatory demented patients are included in the trial on the basis that induction and dose titration are done within a medically supervised environment. As soon as the patient reaches a steady state plasma level at his/her individual highest therapeutic dose tolerated the patient may be discharged and continue in the study as an outpatient.
2. Institutionalised patients which are more severely impaired are enrolled. Although it may not be possible to show any positive effects on the symptoms of AD in these patients, valuable insights into the nature of the drug's dose-related toxicities will be obtained.

If enough safety information has been obtained, Phase II studies may be conducted in an outpatient setting. Generally, the FDA recommends that the study population should be free of concomitant illnesses and should take no or few other medications. Most importantly, participants should be well enough to co-operate fully. Although these criteria are not representative for elderly demented patients, the Agency recommends to study any new AD therapy in only mildly affected patients.

During the entire clinical development programme a minimum of 1.000 patients should be exposed for several weeks to doses within the recommended therapeutic

window. Of these, approximately one third or more should have been on doses at or above the median recommended dose for a period of 6 months to one year.

The draft guideline encourages the applicant to seek continuous scientific advice from the Agency for the development of new anti-dementia treatments.

Safety Assessment

Each patient should undergo a comprehensive physical (blood chemistry, blood counts, urine and stool analysis, ECGs) and neurological examination before, during and after exposure to the test compound.

Study duration of Phase II

No recommendation is given on the study duration required to establish efficacy. However, the FDA points out that a study duration of 3 months may most likely not be judged as adequate to support an anti-dementia claim. Statistically significant effects may only be determined after study periods of 6 months or longer.

Phase III

The study population included in Phase III trials should be representative for the targeted patient population. Regular safety assessments prior to exposure to the investigational drug and at regular intervals during the study period must be performed. Open label or re-randomised follow-up studies are recommended to obtain information on the duration of the treatment effect.

### 4.2.2 Paediatric Assessment Waiver

The Paediatric Research Equity Act (PREA) became law in December 2003 and was reauthorised by the FDA Amendment Act in 2007. It requires in Title IV, section 402 that all applications (or supplements to an application) submitted under section 505 of the Code of Federal Regulations (21 CFR) for a new active ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration to contain a paediatric assessment unless the applicant has obtained a waiver or deferral.

In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and paediatric populations. However, if an applicant does not submit a paediatric assessment, he must provide sufficient evidence to the Agency that the indication or condition targeted by the new drug does not occur in the paediatric population. According to PREA, section 402 (2) (A) this is the case if:

- The necessary studies are impossible or highly impracticable because, for example, the number of patients is so small or the patients are geographically dispersed.
- There is evidence strongly suggesting that the therapy would be ineffective or unsafe in the paediatric population.

However, PREA also authorises the FDA to grant a waiver when the drug or biological product is intended for the treatment of an indication that has extremely limited applicability to paediatric patients because the pathophysiology of the disease occurs for the most part in the adult population. A list of adult-related conditions that may be candidates for a disease-specific waiver is given in the draft guideline “How to Comply with the Pediatric Research Equity Act” from September 2005 (Attachment A, “Sample Waiver Request Form”). Alzheimer’s Disease is part of this list.

Consequently, the requirement to submit a paediatric assessment may be waived on the grounds that AD is an adult-related condition.

### 4.2.3 Geriatric Requirements

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) finalised the guideline E7 "Studies in support of special populations: geriatrics" in June 1993. The ICH E7 guideline was published by the FDA in the Federal Register on August 2, 1994 (59 FR 39398) and is applicable to all drugs and biological products. Thus, new drug applications submitted to the FDA should in principle consider the same geriatric requirements in respect to pharmacokinetic studies and drug-drug interaction studies as described in section 4.1.4.

Generally, the CFR mandates an efficacy and safety analysis of new drug applications according to gender, age and race. In addition to the adoption of the ICH E7 guideline in 1994, the FDA established the geriatric use subsection within the specific requirements on content and format of labelling for human prescription drugs in 1997. According to 21 CFR 201.57 (f) (10), more complete information based on specific clinical data about the use of a drug or biological product in the elderly (persons aged 65 years and over) must be included as a part of the precautions section in the labelling for human prescription drugs.

The 'geriatric use' subsection should cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. The data necessary to comply with these requirements must be obtained either from controlled studies that are available to the sponsor or pertinent information from well-documented studies obtained from a literature search.

## *4.3 Comparison of the Guidance provided by the EMEA and the FDA*

In principle, the regulatory guidance provided by the EMEA based on the "Guideline on Medicinal Products for the Treatment of Alzheimer's Disease" (CPMP/EWP/553/95) from 1998 and the FDA based on the draft guideline "Guidelines for the Clinical Evaluation of Antidementia Drugs" from November 1990 is relatively similar. The definition of AD is founded on the same diagnostic criteria, namely the DSM-IIIR. AD is understood to be a progressive disease with an irreversible decline in intellectual and cognitive abilities.

However, in addition to this basic definition given above, the EMEA stresses changes in the personality and abnormalities in the behaviour of AD patients. These additional aspects of AD are also reflected in the endpoints recommended to prove therapeutic efficacy. Both regulatory authorities ask for two primary end-points. But the EMEA recommends a cognitive and a functional endpoint while the FDA measures efficacy on the basis of cognitive performance and overall clinical assessment (cognitive and global endpoint). The functional domain is not mentioned by the FDA.

Both guidelines focus on symptomatic treatment. The FDA defines improvement of AD symptoms as improvement of the ability to learn new and retrieve old information. As the EMEA also considers personality changes and behavioural aspects, therapeutic efficacy includes improvement in these domains as well.

Furthermore the draft guideline from the FDA does not provide specific recommendations on the measurement tools acceptable to show efficacy. This may

be due to the date the draft was written. In 1990 not much experience on the use of measurement tools was available. Thus, each applicant was requested to validate the use of the chosen instrument in the setting of his clinical trial. The revised guideline from the EMEA can base its recommendation on more than 15 years of clinical trial experience with various measurement tools. Thus, some guidance is provided on which tools to use for the cognitive, functional and global domain.

The most important difference between guidance provided by the two regulatory authorities seems to concern the development of disease-modifying therapies. Not much was known about the aetiology of AD in the early 1990s. Thus, the draft guideline from the FDA focuses exclusively on symptomatic treatment. Even symptomatic treatments were just in clinical development with the first one, tacrine, not approved before 1993 (see chapter 5). Although these circumstances applied also to the original guideline from the EMEA, the recently adopted revision has dedicated a major part of the guideline to this topic of disease-modifying treatments (see chapter 4.1.2). Thus, the EMEA provides regulatory guidance to companies developing new anti-Alzheimer treatments, which is much more up-to-date. It will be interesting to see in the near future to which extent the FDA will accept such development programmes which have been designed according to the European recommendations.

# 5 Requirements Fulfilled for Approval by Already Marketed Alzheimer's Therapies

As discussed in chapter 2, there are four AChE inhibitors and one NMDA receptor antagonist approved for the treatment of AD. The first medication available to AD patients was tacrine, which was approved in the US in 1993 and in some European countries in 1995. Due to its low oral bioavailability, its short half-life requiring dosing four times daily and its hepatotoxicity, however, it could not compete with the AChE inhibitors which obtained approval in the following years. The second approval was granted for donepezil in the US in 1996 and in Europe in 1997, followed by the approval for rivastigmine in Europe in 1998 and the US in 2000. The most recently approved AChE inhibitor is galantamine. Market authorisation was granted in Europe in 2000 and the US in 2001.

memantine, the only NMDA receptor antagonist available for the treatment of moderate to severe AD, was approved in Europe in 2002 and in the US in 2003.

## *5.1 Acetylcholine Esterase (AChE) inhibitors*

### 5.1.1 Europe

According to the European Public Assessment Report published on the website of the EMEA, rivastigmine (Exelon®) was first approved by the European Commission on May 12, 1998 as an immediate-release capsule formulation for the treatment of patients with mild to moderately severe AD. An oral solution and a transdermal patch formulation were approved by the EC as alternative galenic formulations on June 2, 1999 and March 4, 2004 respectively. The therapeutic indication of rivastigmine was extended to include the symptomatic treatment of mild to moderately severe dementia associated with Parkinson's Disease on February 28, 2006.

Representative for the class of AChE inhibitors, the regulatory requirements to prove clinical efficacy in Europe of the originally approved rivastigmine capsules as symptomatic treatment for patients with mild to moderate AD are described below. As

described in chapter 2.1, the systematic review of the available AChE inhibitors by the Cochrane Collaboration revealed no significant differences concerning safety and efficacy of the three second-generation AChE inhibitors, donepezil, rivastigmine and galantamine. Thus, the choice to discuss the regulatory requirements fulfilled to prove efficacy using the example of rivastigmine was made arbitrarily.

A total of 39 clinical studies were submitted in the application for marketing authorisation by Novartis who is the holder of the license:

Phase I 17 clinical pharmacology studies.

Phase II 6 therapeutic efficacy studies of which 3[10] were conducted in Japanese patients (2 open and 1 double-blind study).

Phase III 16 therapeutic efficacy studies.

***Phase II***

The three placebo-controlled Phase II studies which were considered in the assessment for approval included a total of 566 patients and lasted between 10 and 18 weeks. The main purpose of these studies was to determine the maximum tolerated dose and the optimal dosing regimen. The MTD was determined as 12 mg/day and although t.i.d. administration seemed to be associated with slightly less undesirable effects in one of the studies, b.i.d. administration was considered to be optimal.

Statistically significant efficacy versus placebo of a global primary endpoint could be shown in two of the three studies. In one study the CGI-C was used and in the other study the CIBIC-Plus. Several measurement tools were used as secondary endpoints, like MMSE, Fuld Object Memory Evaluation, Digit Symbol Substitution Test, Benton Visual Retention Test, Trial Making Test and Nurse Observation Scale for Geriatric Patients.

***Phase III***

Four of the Phase III studies were regarded as pivotal efficacy studies. These were all randomised, placebo-controlled, multi-centre studies with a duration of 26 weeks (see table below taken from the European Public Assessment Report published on the website of the EMEA). Two of the studies and the US centres of a third study had an open-label extension phase of two years while the remaining study and the European centres of one study had an open-label extension phase of six months. Efficacy assessment was based on the data obtained from more than 2.100 AD patients.

[10] The three Japanese studies were not included in the assessment for approval.

**Table:** Main Phase III placebo-controlled studies (radomised, multicentre, double-blind studies in parallel groups)

| Study | Description | Treatment (mg/day) *Fastest titration rate* | Duration (weeks) | No. of patients randomised | |
|---|---|---|---|---|---|
| | | | | rivastigmine | placebo |
| B351 | Study comparing the efficacy and safety of three doses of rivastigmine (3 mg/day, 6 mg/day, 9 mg/day) with placebo. | Fixed dose: 3, 6 and 9 (b.i.d) *1mg/day/week* | 26 | 529 (175/176/178) | 173 |
| B352 | Study to compare the efficacy and safety of 1-4 mg/day rivastigmine with 6-12 mg/day rivastigmine with placebo. | Individual MTD, 1-4 and 6-12 (b.i.d) *1-1.5mg/day/week* | 26 | 434 (233/231) | 235 |
| B303 | Study to compare the efficacy and safety of 1-4 mg/day rivastigmine with 6-12 mg/day rivastigmine with placebo. | Individual MTD, 1-4 and 6-12 (b.i.d) *1-1.5mg/day/week* | 26 | 486 (243/243) | 239 |
| B304 **Interim Safety Report** | Study comparing rivastigmine 2-12 mg/day, given in a tid or bid regimen, with placebo. | Individual MTD, 2-12 (b.i.d or t.i.d) *1-1.5mg/day/week* | 26 | 229 (118/111) | 117 |

Patient Population:

Patients included in the Phase III programme were at least 50 years old and fulfilled the following criteria:

- DSM-IV
- NINCDS-ADRDA
- MMSE score between 10 and 26 (both included)

The severity of AD was determined using the global deterioration scale of Reisberg. Patients with abnormal laboratory parameters, indicative for impaired renal or hepatic function, and severe progressive disease were excluded.

Concomitant Medication:

Generally, therapies influencing the efficacy assessment due to an effect on alertness, intellectual function and behaviour were not permitted. However, chloral hydrate for occasional insomnia or agitation was allowed. In two studies short-acting benzodiazepines for occasional insomnia or agitation and haloperidol against hallucination were permitted.

Efficacy:

Efficacy was assessed by improvement of symptoms in the cognitive, functional and global domain after 26 weeks. In all Phase III studies cognitive and the global endpoints were used as primary efficacy measures combined with various secondary endpoints (see table below).

| ENDPOINT | DOMAIN | MEASUREMENT TOOL |
|---|---|---|
| Primary | Cognitive | ADAS-cog |
| | Global | CIBIC-Plus |
| Secondary | Functional | Progressive Deterioration Scale (PDS) |
| | Other (severity of AD) | MMSE |
| | Other (severity of AD) | Global deterioration scale of Reisberg (GDS) |

Statistically significant differences in efficacy compared to placebo could be shown for the 6 to 12 mg/day rivastigmine treatment group after 26 weeks. With regard to the cognitive endpoint measured by ADAS-cog the mean difference in the pooled analysis was 2.4 points and for the global endpoint measured by CIBIC-Plus 0.3 points.

Due to these moderate effects the Committee for Proprietary Medicinal Products (CPMP) which is called today Committee for Medicinal Products for Human Use (CHMP) requested a responder definition of at least a 4-point improvement in ADAS-cog and an improvement (score <4) on CIBIC-Plus. Compared to placebo, twice as many patients in the active treatment group fulfilled these criteria (8% versus 4%) with a statistical significance of $p<0.001$.

Safety:

The safety assessment of rivastigmine was based on data from 3.006 patients who received at least one therapeutic dose of the medicinal product and had a subsequent safety evaluation. In total, 1.249 patients were treated with rivastigmine for more than 6 months (for patient numbers per dose groups see table below) and 220 patients received the compound for more than one year.

| Dose | ≤ 3 mg/day | 3-6 mg/day | 6-9 mg/day | 9-12 mg/day |
|---|---|---|---|---|
| Number of Patients | 128 | 513 | 248 | 360 |

In Phase III controlled clinical trials the highest proportion of withdrawals for adverse events was due to gastro-intestinal disorders, such as nausea and vomiting. However, the percentage of withdrawals seemed to decrease with the duration of exposure and the cumulative risk reached a plateau after 3 months. As the gastro-intestinal symptoms normally responded to dose reduction and no clinically important effects on other safety parameters, such as laboratory values, ECGs or cardio-respiratory vital signs were observed, the safety assessment was positive.

Interactions:

If rivastigmine is taken together with food, the absorption of the active ingredient is slightly delayed. The maximal serum concentration is decreased while the extent of absorption is increased.

No pharmacokinetic interactions were observed in drug interaction studies with digoxin, warfarin, diazepam and fluoxetine. As rivastigmine is only minimally metabolised by cytochrom P450, no metabolic interactions are expected.

Special populations:

Clearance of a single oral dose of rivastigmine was approximately 30% lower in elderly healthy volunteers (older than 60 years) compared to younger healthy volunteers. Bioavailability did not change with age but gender and body surface area were found to influence plasma levels of the compound. However, elimination was not prolonged and the drug showed no accumulation.

Plasma levels were twice as high in patients with renal impairment compared to healthy subjects and increased exposure could also be observed in cirrhotic patients. Thus, a statement in the summary of product characteristics (SPC) was included to carefully titrate rivastigmine in these patient groups according to their individual tolerability.

### 5.1.2 USA

According to publicly available information on the FDA's internet site "FDA Approved Drug Products", two alternative formulations of rivastigmine, namely an immediate-release capsule and an oral solution formulation, were first approved by the FDA on April 21, 2000 for the treatment of mild to moderate dementia of the Alzheimer's type. The therapeutic indication of rivastigmine was extended to include the symptomatic treatment of mild to moderate dementia associated with Parkinson's Disease on June 27, 2006. A transdermal patch formulation was approved by the Agency as additional presentation on July 6, 2007, more than three years later than in Europe (see chapter 5.1.1).

Representative for the class of AChE inhibitors, the regulatory requirements to prove clinical efficacy of the rivastigmine formulations (capsules/oral solution) originally approved in the US for the treatment of mild to moderate dementia of the Alzheimer's type are described below.

From the different reviews (clinical pharmacology, medical, statistical) provided by the FDA on the internet site related to the approval history of rivastigmine it is not entirely clear how many Phase I, II and III studies were submitted with the original New Drug Application (NDA) in July 1997. However, it seems likely that the data set was comparable to the one submitted to the EMEA in April 1997. Although the EMEA approved the medicinal product in May 1998, the FDA sent out a "not-approvable letter" based on unresolved concerns that the effective dose of rivastigmine may be associated with an increased risk of mortality. Thus, additional data or different analyses of the original data needed to be provided during the following years until in May 1999 an "approvable letter" was issued by the Agency and the compound was finally approved in April 2000. These subsequent submissions of safety up-dates were exclusively dedicated to resolve the issue of increased mortality.

However, the assessment of clinical efficacy was based on the same placebo-controlled Phase II and Phase III studies submitted to the EMEA (see chapter 5.1.1). Thus, only aspects different from the EMEA assessment are described below.

Efficacy:

As in Europe, two primary endpoints measured by the ADAS-cog and CIBIC-plus were used in the therapeutic efficacy studies. Further to the secondary endpoints used in Europe, Novartis developed an additional measurement tool which was named “Caregiver Activity Survey (CAS)”. This assessment tool measures the amount of time the caregiver has to spend with the patient to assist in various activities of daily living.

Safety:

According to the end-of-phase 2 meeting between Novartis and the FDA, the safety assessment should have been based on approximately 2.000 patients with any exposure to the drug and a few hundred patients with greater than six months of exposure. Due to the safety concerns described above, safety data needed to be provided on a continuous basis (see medical review by R.B. Mani, HFD-120, pp 29). The Agency’s safety assessment included several additional studies provided during the assessment period. These additional studies were:

- 3 JP Phase II studies (controlled)
- 5 US Phase III studies (uncontrolled)
- 2 US Phase IIIb studies (controlled)
- safety data of 3 international studies and 2 US studies were considered but not included in the safety analysis on which the approvable letter was based.

In summary, the safety data of 5297 patients which received at least one dose of rivastigmine were analysed. This corresponds to 5.713 patient years of exposure. Thus, the safety data of 2.291 patients more were analysed by the FDA compared to the EMEA. It is not apparent from the medical review how many of these patients were treated with the therapeutic dose for more than six months. Nevertheless, these data could resolve the Agency’s safety concerns and rivastignine was approved in April 2000. However, a post approval commitment had to be made.

The most common adverse effect associated with the use of rivastigmine (Exelon®) concerns the gastro-intestinal tract (nausea and vomiting). Thus, Novartis committed itself to conduct additional analyses of existing data to compare the incidence of nausea, vomiting and weight loss associated with the regimen recommended in the final label to that resulting from a dosing regimen with smaller dosing increments (e.g. 1 mg per day in divided doses) in the therapeutic range of 6 to 12 mg per day. These analyses had to be provided within six months. If not conclusive, the design of clinical trials to address this issue will be discussed with the FDA.

Special Populations:

No specific pharmacokinetic studies were conducted to investigate the effect of gender and race on the disposition of the compound, but a population pharmacokinetic analysis indicated that there was no effect on clearance of rivastigmine.

Nicotine use increased the oral clearance of rivastigmine by 23%.

### 5.1.3 Conclusion

In principle, the regulatory requirements fulfilled by rivastigmine (Exelon®) are identical in both regions. Efficacy was based on the same clinical trials submitted and assessed using the same endpoints and measurement tools. The label is for the same indication, namely mild to moderately severe AD. During an oral explanation meeting in August 1999, the FDA explained that there was no difference between the term mild to moderately severe AD and mild to moderate AD (see medical review by R.B. Mani, HFD-120, p. 33). Furthermore, the recommended titration scheme as well as the therapeutic dose range of 6 to 12 mg per day are identical.

However, while the medicinal product was approved in Europe by the EC within one year, time to approval by the FDA was more than three years. The FDA had more safety concerns because of an initially unresolved risk of increased mortality. Several subsequent submissions of safety data and safety up-dates were required to finally resolve this issue.

## *5.2 NMDA Receptor antagonist*

### 5.2.1 Europe

As discussed in chapter 2, there is only one other treatment option for AD than AChE inhibitors, namely the NMDA receptor antagonist memantine. This compound was already developed and patented by Eli Lilly in 1968. Subsequently, memantine was licensed-in for the German territory by the pharmaceutical company Merz. They developed the compound in collaboration with Neurobiological Technologies. Memantine was finally approved nationally in Germany as Akatinol® in 1982 for the treatment of Parkinsonism, cerebral and peripheral spasticity and organic brain syndrome. Later, Merz developed as well as patented the use of memantine for the treatment of AD and licensed the rights for this indication to Forest Laboratories for the US and to Lundbeck A/S for several European Countries.

According to the European Public Assessment Report published on the website of the EMEA, this medicinal product was first approved by the European Commission on May 15, 2002 - only seven months after the application for marketing authorisation was submitted in parallel by the pharmaceutical companies Merz and Lundbeck A/S. Memantine (Axura®, Ebixa® respectively) is available as immediate-release film-coated tablets and as oral drops solution and is indicated for the treatment of moderately severe to severe AD. In October 2005, the therapeutic indication was extended by a variation to include moderate to moderately severe AD.

The initially approved dosing regimen was 10 mg twice daily. In May 2008, a type II variation was approved by the European Commission to replace the originally recommended 10 mg twice-daily posology of memantine with a 20 mg once-daily dosing regimen.

As memantine was already approved nationally in Germany as Akatinol® (see above), a total of 25 studies including 4.428 patients were mentioned in the dossiers submitted to the EMEA. However, only four Phase III studies provided data in relation to the efficacy and safety of memantine in moderately severe to severe AD. Even so, the safety data obtained in the 21 pilot studies involving small numbers of patients from patient populations different to those intended were used as supportive evidence in the safety assessment of the compound.

***Phase III***

Four newly conducted Phase III studies were submitted to the EMEA. However, only one of these was dedicated to study only AD patients. This study was actually designed according to CPMP scientific advice requested in 1998. The other clinical trials were based on patients suffering from vascular dementia (VaD) and one study had a mixed patient population of approximately 50% AD patients and 50% VaD patients. All of the Phase III trials were randomised, double blind and placebo-controlled with a duration of 28 weeks, except for the trial with the mixed patient population which lasted only 12 weeks. After the trial all patients were given the opportunity to enter an additional 6 months open-label treatment period. Efficacy assessment was based on the data obtained from only 331 AD patients.

Patient Population:

AD Patients included in the pivotal Phase III study designed according to CPMP scientific advice were at least 50 years old and fulfilled the following criteria:

- DSM-IV
- NINCDS-ADRDA
- MMSE score between 3 and 14 points (compared to scores between 10 and 26 for mild to moderate AD)

The severity of AD was further determined using the global deterioration scale of Reisberg (at least stage 5 or 6) and the Functional Assessment Staging Scale (FAST, at least stage 6a)[11].

To distinguish the AD patients form the VaD patients in the study with the mixed patient populations the Hachinski Ischemic Scale (HIS)[12] was employed. This scale is utilising 9 items and scores lower than four are indicative for AD while scores greater than 7 are indicative for VaD. AD patients identified via the HIS were inpatients between 60 and 80 years and fulfilled the following criteria:

- DSM-III-R
- MMSE score < 10
- Duration of dementia or symptoms > 12 months

The severity of AD was further determined using the global deterioration scale of Reisberg (at least stage 5 to 7) and Clinical Global Impression-Severity scale (CGI-S)[13] (5 to 7 points).

Concomitant Medication:

Only medicinal products which did not influence alertness, intellectual function and behaviour were allowed. However, patients receiving inadmissible medication, such

[11] Instrument to assess functional decline with seven stages: 1=normal adult, 2=normal older adult, 3=early Alzheimer's Disease, 4=mild Alzheimer's Disease, 5=moderate Alzheimer's Disease, 6=moderately severe Alzheimer's Disease, 7=severe Alzheimer's Disease.

[12] Instrument consisting of 9 items (abrupt onset, stepwise deterioration, fluctuating course, somatic complaints, emotional incontinence, history of hypertension, history of stroke, focal neurological symptoms, focal neurological signs). Each item is assigned a pre-specified score of 1 or 2. Maximum score is 14 with higher scores indicative for VaD.

[13] CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis (1=normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill).

as other investigational drugs, anticonvulsants, anti-Parkinson, hypnotics, neuroleptics/antipsychotics, AChE-inhibitors) could be included after a wash-out period of 30 days. For investigational drugs this period was extended to 60 days.

Efficacy:

In both Phase III studies efficacy was assessed by improvement of symptoms in the global and functional domain. No cognitive domain was chosen as primary endpoint because cognition would have been difficult to assess in a patient population with such advanced dementia. The primary endpoints from the global and functional domain were combined with several secondary endpoints (see table below).

| ENDPOINT | DOMAIN | MEASUREMENT TOOL |
|---|---|---|
| **Endpoints in the study only including AD patients** | | |
| Primary | Global | CIBIC-Plus |
| | Functional | ADCS-ADL |
| Secondary | Functional | FAST |
| | Functional | Modified ADCS-ADL |
| | Cognitive | Severe Impairment Battery (SIB)[14] |
| | Other (severity of AD) | MMSE |
| | Other (severity of AD) | GDS of Reisberg |
| | Other (severity of AD) | Neuropsychiatric Inventory (NPI)[15] |
| | Other (severity of AD) | Resource Utilisation and caregiver burden (RUD)[16] |

[14] SIB includes very simple tasks which are presented with gestural cues. The battery is divided into 9 sub-scales, assessing attention, orientation, language, memory, praxis, visospacial perception, construction, social skills and orientation to name. Total scores range from 0 to 100 points with higher scores indicating better cognitive function.

[15] Validated instrument assessing 10 neuropsychiatric domains (delusions, hallucinations, anxiety dysphoria/depression, agitation/aggression, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor activity). Frequency is rated 1 to 4, severity is scored 1 to 3. Rating is based on interviewing a caregiver. “Severity x frequency” is calculated for each domain and summed-up. Maximum score is 120 with higher scores indicating greater behavioural abnormality.

[16] Designed to assess caregiver burden based on a structured interview measuring the time invested to help with basic activities of daily living like toilet visits, eating, dressing, grooming, walking and bathing and instrumental activities of daily living like shopping, food preparation, housekeeping, laundry, transportation, taking medication and managing financial matters.

| Endpoints in the study including a mixed patient population (AD and VaD) | | |
|---|---|---|
| Primary | Global | CGI-C |
| | Functional | Rating Scale for Geriatric Patients (BGP[17]), sub-scale "care dependence" |
| Secondary | Functional | BGP, global score |
| | Functional | Instrumental ADL |
| | Other (severity of AD) | CGI-S |

Statistically significant differences in efficacy compared to placebo in the pivotal trial could initially only be shown for the functional domain while the global domain showed merely a positive trend after 28 weeks. However, upon re-analysis using the CPMP Guideline "Points to Consider on Missing Data" (CPMP/EWP/1776/99 draft) this positive trend became statistically significant. Furthermore, the cognitive secondary endpoint SIB showed also statistical significance in favour of memantine. Interestingly, the compound could sustain its efficacy during the extension phase over a cumulated treatment period of 12 months.

Statistical significance could also be shown for both the functional and the global primary endpoint in the AD sub-population of the clinical trial which included not only 79 AD but also 88 VaD patients. Although this trial used only half of the recommended therapeutic dose and lasted only three months, the data were accepted by the CPMP as supportive evidence of efficacy.

Safety:

As memantine was approved already nationally in Germany in 1982, safety data were available from 32 completed clinical trials in various indications. 2.863 participants of which 2.231 were patients suffering from some form of dementia were included in the safety assessment. 1.943 study participants received at least one dose of memantine and a total of 1.185 patients were treated with the recommended therapeutic dose of 20 mg per day (see table below).

| Dose | < 20 mg/day | 20 mg/day | > 20 mg/day |
|---|---|---|---|
| Number of Patients | 398 | 1.185 | 360 |

In Phase III controlled clinical trials the most frequent adverse events which could be attributed to memantine were dizziness, headache and fatigue/tiredness. Surprisingly, agitation was reduced by 4% with the compound compared to placebo.

At the time of approval there were still some pending preclinical issues, such as putative harmful effects of the small amounts of memantine excreted via the lacrimal

[17] Clinician-based measure consisting of 35 items which assess behaviour (including mood), basic cognitive functions, mobility and activities of daily living. "Care dependency sub-scale" comprises 23 items, each scoring from 0 to 2 with 0=no assistance, 1=limited assistance and 2=frequent assistance. Maximum score is 46 with higher scores indicating worse level of functioning.

gland and an increased prevalence of pulmonary foamy macrophages. Furthermore animal experiments revealed a potential risk for neurological toxicity as so-called Olney-type lesions were found. Therefore, these issues had to be addressed by long-term safety monitoring of ocular, pulmonary and neurotoxic side-effects. Actually, Lundbeck proposed to conduct additional clinical studies of long duration in patients with glaucoma, neuropathic pain and mild AD.

Interactions:

In vitro testing did not reveal any interactions between memantine and numerous enzymes commonly involved in drug metabolism, such as CYP-enzymes. In clinical trials, no drug interactions were observed with acetylsalicylic acid, tocopherol, donepezil (AChE-inhibitor), paracetamol, and chloral hydrate. However, due to the chemical relationship to amantadine, which is also a NMDA receptor antagonist, the concomitant administration of memantine and amantadine should be avoided because this could bear the risk of pharmacotoxic psychosis. Furthermore, effects of anticholinergic agents, such as L-dopa or dopaminergic agents, may be enhanced while the effects of barbiturates and neuroleptics may be attenuated.

No food interactions were found with memantine. Thus, the compound may be administered with or without food.

Special Populations:

As memantine is mainly excreted unchanged via the kidneys, a significant correlation between creatinine clearance and total renal clearance of the medicinal product was observed. Thus, dose adjustments may be necessary in patients with moderate and severe renal impairment.

No special precautions need to be taken in patients with mild or moderate hepatic impairment.

### 5.2.2 USA

After memantine's approval in Europe in May 2002, a NDA was submitted to the FDA for memantine (Namenda®) by Forest Laboratories in December of the same year. According to the publicly available information on the FDA's internet site, the compound was first approved as an immediate-release tablet formulation for the treatment of moderate to severe dementia of the Alzheimer's type in October 2003. An application for the alternative formulation as oral solution was submitted in May 2003. However, this alternative formulation, which had already been marketed in Europe since mid 2002, was not approved by the FDA before April 2005 because the FDA was not satisfied with the reliability of measuring the individual doses (see medical review, HFD-120, NDA 21627, R.B. Mani, 10.02.2004).

From the safety review (G.Boehm, NDA 21-487, 20.08.2003) provided by the FDA on the internet site related to the approval history of memantine it appears that Forest Laboratories submitted the same data set as was submitted to the EMEA in October 2001. Additionally, one Phase III efficacy study in AD, two Phase II/III studies in neuropathic pain and data available from studies ongoing during the time of NDA evaluation as well as post marketing reports from Europe were submitted on a continuous basis.

In the following paragraphs the additionally submitted data and topics which differ between EMEA and FDA concerning the assessment of the marketing application are discussed.

Concomitant Medication:

Only medicinal products which did not interfere with the investigational drug by influencing e.g. alertness, intellectual function and behaviour were allowed. Such medicinal products were cardiac glycosides, anti-hypertensives and oral anti-diabetics. However, the dosage of the concomitant medication was required to be kept constant during the clinical trial.

Prohibited medication, such as anticonvulsants, monoamine oxidase inhibitors, neuroleptics, tricyclic anti-depressants, nootropics or agents for promotion of cerebral circulation, hypnotics except for chloral hydrate or benzodiazepines with short half-lives needed to be discontinued at least 14 days prior to the study.

In one trial memantine was used as add-on therapy to the AChE inhibitor donepezil. However, patients were required to be on a stable dose of the drug and the dosage needed to be kept constant during the clinical trial.

***Phase III***

The same four Phase III studies as in Europe were submitted. Furthermore, one additional Phase III trial in patients with moderate to severe AD was submitted in which memantine was studies as add-on to the AChE inhibitor donepezil.

Patient Population (of the additional Phase III study):

The 404 AD patients enrolled in the study fulfilled the following criteria:

- NINCDS-ADRDA
- MMSE score of 5 to 14
- Treatment with donepezil for at least six months, with a stable dose for at least three months

Efficacy:

The two studies conducted in patients with VaD were not considered for the assessment of efficacy in AD because of the different indication (R.B. Mani, medical review, HFD-120, NDA 21-487, 02.10.2003). Furthermore, the FDA came to the conclusion that the clinical trial conducted in a mixed patient population of approximately 50% AD patients and 50% VaD patients provided less convincing support for the efficacy of memantine. The main arguments for rejecting this study were the facts that patients were not diagnosed using standard criteria like NINCDS-ADRDA but HIS, that the study had no cognitive primary endpoint and that only 52% of the patients underwent brain imaging to exclude other forms of dementia.

Most importantly, the pivotal AD trial from the European submission was initially not accepted by the FDA because the Agency did not accept the applicant's rationale for not taking a cognitive endpoint as primary outcome measure in patients with moderate to severe AD (see chapter 5.2.1). However, as this trial showed statistically significant improvement in favour of memantine of a cognitive secondary endpoint (SIB), the FDA accepted this study as one of the two required pivotal trials.

Thus, the main trial in support of efficacy was a 24 week randomised, double-blind, placebo-controlled study of memantine in comparison with placebo in patients with moderate to severe AD who were already taking a stable dose of the AChE inhibitor donepezil. According to the regulatory requirements of the FDA, the two primary endpoints were from the cognitive domain (SIB) and from the functional domain (ADCS-ADL). Additionally, several secondary efficacy measures were analysed.

Although the mean change of both primary efficacy variable compared to the baseline assessment was only small, the results were statistically significant.

Safety

In addition to the safety data from 32 completed trials which had been submitted to the EMEA, Forest Laboratories submitted safety data of another Phase III trial in dementia including 403 patients and two Phase II/III trials in neuropathic pain including 122 and 418 patients respectively. Furthermore, all safety data from post-marketing reports in Europe as well as the safety data from ongoing trials were submitted.

Additional adverse events observed in the US with an at least 2% higher frequency than with placebo were pain, hypertension, and constipation.

While the EMEA requested further safety data on ocular, pulmonary and neurotoxic side-effects, the FDA was concerned about ocular and cardio-vascular (QT-interval prolongation) side effects. Consequently, the following post approval commitments were laid down in the approval letter:

- Reanalysis of the available ECG interval data
- Submission of additional eye examination results from ongoing studies
- Submission of the final report of the ongoing renal impairment study
- Conduct of a study in subjects with moderate hepatic impairment.

### 5.2.3 Conclusion

Comparing the label of memantine in Europe and the US it seems that the EMEA differentiates more stages of AD than the FDA. This becomes particularly apparent if one looks at the type II variation approved in October 2005 by the European Commission. This variation extended the therapeutic indication from “moderately sever to severe AD” to include also “moderate to moderately severe AD”.

While the regulatory requirements fulfilled for approval of the AChE inhibitors were comparable between Europe and the US this is not the case for memantine. Although the EMEA recommended using a cognitive and a functional endpoint as primary efficacy measure, the Agency accepted also clinical trials with a functional and a global endpoint in the case of advanced AD. This is well in line with the recommendations laid down in the “Guideline on Medicinal Products in the Treatment of Alzheimer’s disease and other Dementias” (CPMP/EWP/553/95 Rev. 1). Contrary to the EMEA, the FDA only accepted clinical trials for the efficacy assessment if one of the two primary endpoints was from the cognitive domain, independent of the stage of AD to be claimed.

# 6 Outlook on New Therapies in Development for Alzheimer's Disease

## *6.1 Tramiprosate (Alzhemed)*

The glycosaminoglycan (GAG) mimetic tramiprosate, also known as Alzhemed®, was developed by Neurochem, now Bellus Health, for the potential treatment of AD. GAGs have been demonstrated to play a role in the conformational changes undergone by amyloid beta as it aggregates into beta-sheet containing amyloid plaques (McLaurin et al. 1999). Additionally, it was shown that GAGs seem to be involved in the formation of neurofibrillary tangles (Hernandez et al. 2002).

Tramiprosate is an orally administered, small organic molecule that binds to soluble A-beta 42 thereby preventing GAGs from binding to amyloid beta and thus preventing them from promoting beta–sheet and amyloid plaque formation. The rationale behind targeting GAGs is that inhibiting amyloid plaque formation may potentially reduce downstream neurotoxic effects such as neuro-inflammation or oxidative stress-mediated neurotoxicity.

A randomised, double-blind, placebo-controlled Phase II trial with 58 participants suffering from mild to moderate AD showed promising results. Patients received 50, 100 or 150 mg tramiprosate twice daily for three months and could continue for additional 17 months in an open-label follow-up trial. The trial demonstrated that the compound was safe and well tolerated and that it reduced the level of amyloid beta in the CSF of AD patients. Furthermore, mean Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) and Mini-Mental State Examination (MMSE) scores remained near baseline in the mild AD group over the 20 months of follow-up (Aisen et al. 2006).

Subsequently two big Phase III trials were conducted; one in North America and one in Europe. The North American study was a multicentre, randomised, double-blind, placebo-controlled, three-armed and parallel-designed, 18-months Phase III clinical trial. 1.052 patients with mild to moderate AD were recruited across 67 sites in Canada and the US. Patients were randomised to receive either placebo or one of the two doses of tramiprosate (100 mg or 150 mg twice daily). All patients received standard symptomatic AD therapies like AChE inhibitors during the clinical trial. However they were required to be on a stable dose of such therapies for at least four months prior to the initial screening visit of the trial. After completion of the trial, patients were eligible to receive twice daily 150 mg tramiprosate in an open-label extension study which was initiated in May 2006.

The European study was designed in the same way as the North American study. As of August 2007, 966 patients suffering from mild to moderate AD had been enrolled at 69 study centres in ten European countries.

Despite the descriptive data showing numerical differences, the North American Phase III clinical trial for tramiprosate did not demonstrate a statistically significant difference in favour of the compound with respect to the co-primary clinical efficacy endpoints composed of ADAS-cog(1) and CDR-SB(2) over 18 months of treatment. Interestingly, a substantial difference observed in hippocampal volume did approach statistical significance (Company's Press Release of August 27, 2007). In light of the North American Phase III results, Neurochem decided not only to discontinue the European Phase III trial early but also to terminate its efforts to obtain regulatory approval for tramiprosate (company's press release of November 8, 2007).

Looking at the clinical development programme, it seems the clinical trials were designed well in line with the regulatory requirements for the development of Anti-Alzheimer therapies. Patient numbers included in the studies and trial duration should have been sufficient to study the compound's effect. Also the clinical endpoints were chosen according to the guidance provided by the regulatory authorities. However, due to the positive trend observed in the Phase III studies on top of the standard symptomatic treatment the company felt encouraged to promote its next generation lead candidate NRM-8499 which is a pro-drug of tramiprosate and achieved a five-fold higher brain concentration in animal studies.

However, this means that it will remain elusive for many more years whether the disappointing Phase III results of tramiprosate were due to the study design or the mechanism of action.

## *6.2 Tarenflurbil (Flurizan®)*

Myriad Genetics and its licensing partner Lundbeck were developing tarenflurbil, also known as Flurizan®, for the potential treatment of AD. It is the R-enantiomer of the racemic flurbiprofen which is a NSAID that was launched by Pfizer under the trade name Ansaid at the end of the 1970s. Tarenflurbil lacks significant cyclooxygenase-inhibiting activity and, therefore, has the advantage of reduced gastrointestinal and other side effects as opposed to NSAIDs with cyclooxygenase-inhibiting activity. The compound is an allosteric modulator of gamma-secretase. Therefore, it lowers amyloid beta production by selectively modulating, but not inhibiting, gamma-secretase activity to shift cleavage of APP away from A-beta 42 towards shorter, less toxic peptide fragments (Seow and Gauthier 2007). Consequently, the cascade of amyloid accumulation with subsequent plaque formation and neurodegeneration may be inhibited. Most importantly, selective allosteric modulation of gamma-secretase may allow for the enzyme to maintain activity for the other biological effects like the notch signalling pathway.

Preliminary results from a randomised, double-blind, placebo-controlled Phase II trial with 207 participants suffering from mild to moderate AD did not achieve statistical significance. The three primary endpoints of the Phase II study were the Alzheimer's Disease Cooperative Study - Activities of Daily Living inventory (ADCS-ADL), CDR-SB, and the ADAS-cog. Patients were randomised to receive either placebo or one of the two doses of tarenflurbil (400 mg or 800 mg twice daily) for 12 months. Subsequently, all patients were offered to participate in an additional 12 months open-label extension trial. Study participants who had previously received placebo were randomised into the 400 mg or 800 mg tarenflurbil twice daily group. However, a positive trend was observed on all three primary endpoints in patients on the 800 mg twice-daily dose (company's press release of May 2, 2005).

Surprisingly, the results of the Phase II follow-on study revealed that study participants with mild AD taking 800 mg tarenflurbil twice daily demonstrated a substantial benefit for each of the three primary endpoints. Furthermore, the occurrence of psychiatric problems, such as agitation, aggression, confusion and depression, was significantly reduced. Also the time to psychiatric event was significantly longer than in the placebo group (company's press release of July 19, 2006).

A global Phase III trial (ActEarliAD) was initiated already prior to the final analysis of the Phase II results. It was designed as a multinational, randomized, double-blind, placebo-controlled study of tarenflurbil in over 800 patients with mild Alzheimer's

disease, who were followed for 18 months. Patients enrolled in the study took either placebo or one of two doses (400 mg or 800 mg) tarenflurbil twice daily. The three clinical endpoints of the study were identical to those of the Phase II trial, namely the ADAS-cog, CDR-SB and ADCS-ADL.

After the final analysis of the Phase II data showing positive results for participants with mild AD taking 800 mg tarenflurbil twice daily, the US study protocol was modified accordingly. The subsequent US Phase III trial was the largest placebo-controlled study ever undertaken of an investigational medicine in patients with Alzheimer's disease, with a total of 1,684 patients enrolled at more than 100 study sites. Patients enrolled in the amended US study took 800mg twice daily of either placebo or tarenflurbil and were followed for 18 months. An interim review of the data after 12 months would have allowed halting the trial early if exceptional results were achieved. As was the case with the Phase II study, all patients in the US Phase III study were permitted to take current standard of care medicines in addition to tarenflurbil or placebo.

However, in June 2008, the company announced that tarenflurbil failed to achieve significance on either of the co-primary endpoints. As a consequence Myriad and Lundbeck decided to discontinue the development of the compound (company's press release of June 30, 2008). As in the case of tramiprosate described in the previous chapter, the clinical development programme was designed according to the regulatory guidance provided by the FDA and the EMEA. Patient numbers, trial duration and clinical endpoints were chosen as recommended in the (draft) guidelines.

## *6.3 Conclusion*

The failure and subsequent discontinuation of clinical development of the two most advanced and supposedly disease-modifying anti-Alzheimer therapies discussed above (see chapter 6.1 and 6.2), was a huge draw-back on the way to improved treatments for this devastating disease. Although the regulatory framework is well defined, it has become more difficult to obtain a marketing authorisation for a new medicinal product to treat AD because the hurdles to show efficacy are higher today. Symptomatic improvement needs to be demonstrated on top of standard of care treatment, namely AChE inhibitors and/or memantine. More importantly, potentially disease-modifying treatments additionally need to demonstrate a correlation between a prospectively defined biomarker and clinically meaningful improvement of the core symptoms of AD (see chapter 4).

Both programmes had raised high hopes to finally validate a disease-modifying mechanism of action. Unfortunately, these hopes were disappointed and further intensive research will be required to achieve a long awaited break-through in the understanding of the pathogenesis of AD und consequently offer a chance to break the current vicious circle.

# 7 Idealised Clinical Development Plan for a Disease-Modifying Anti-Alzheimer Therapy

The analysis of regulatory requirements fulfilled by the already approved Alzheimer therapies indicates that these requirements are in principle relatively comparable in Europe and the US (see chapter 5). However, with the slight exception that it is of utter importance to always lay down a cognitive primary endpoint in the pivotal clinical trials submitted to the FDA to prove efficacy. Although the currently approved Alzheimer therapies are only marginally effective, they are still considered to be the standard of care. Thus, long-term efficacy studies will have to be designed in a way that the investigational drug shows positive effects in an add-on design to standard care, namely stable doses of AChE inhibitors and/or memantine. Furthermore, the available (draft) guidelines make it clear that even for disease-modifying mechanisms approval can only be obtained if the core symptoms of AD are significantly improved.

Taking the above into account, an idealised global clinical development programme for a putatively disease-modifying new AD therapy should be comprised of at least the following studies to comply with the regulatory requirements in Europe and the US:

***Phase I (approximately 24 study participants per trial)***

- Single dose study in healthy volunteers (ADME)
- Single escalating dose study in healthy volunteers (ADME)
- Multiple dose study in healthy volunteers (ADME)

Special Populations:

- Single dose study in healthy elderly volunteers (>60 or >65 years)
- Multiple dose study in healthy elderly volunteers (>60 or >65 years)
- Single dose study in AD patients (>50 years)
- Multiple dose study in AD patients (>50 years)
- Renal impairment study
- Hepatic impairment study

Interaction Studies:

- Food interaction study
- Various drug-interaction studies, especially with drugs frequently used in the elderly, such as anti-hypertensives and other cardiovascular therapies like digoxin and warfarin, anti-diabetics, anti-psychotics like diazepam, anti-depressants like fluoxetine and others. Furthermore, drug interaction studies are required with AChE inhibitors and memantine.

In addition to the actual Phase I studies that need to be planned and conducted other regulatory measures may have to be initiated at this stage of development, such as requesting a waiver for the submission of a Paediatric Investigation Plan (see chapter 4.1.3 and 4.2.2).

***Phase II (between 200 to 400patients per trial)***

Generally, Phase II studies should be double blind, placebo-controlled, parallel group studies which are conducted in one or more study centres and include AD patients well defined according to the target population (e.g. mild to moderate AD according to the diagnostic criteria defined in DSM-III-R and NINCDS-ADRDA). These studies should have a duration of 3 to 6 months. Normally two or more doses of the investigational product are being studied in comparison to placebo to determine the optimal therapeutic dose for the Phase III programme. An open-label follow-up period of up to 12 months would be recommendable.

Primary outcome measures should be from the cognitive domain and from the functional or global domain. Furthermore, for disease-modifying investigational products a suitable biomarker should be defined which can be correlated with the mode of action (e.g. beta amyloid or inflammation parameters). However, to date none of the defined biomarkers used in clinical trials could be correlated with clinical efficacy. For example, with tramiprosate a substantial difference in hippocampal volume was observed between the placebo arm and the active treatment group. Although this difference did approach statistical significance, it did not translate into an improvement of symptoms (see chapter 6.1). Nevertheless, companies are encouraged to develop a new scale or biomarker for the new treatment approach in development. However, this has to be planned early during Phase I to allow for validation during Phase II. Such a new scale or biomarker must be fully validated to be acceptable for a pivotal Phase III trial.

Another example is the vaccine, AN1792, developed by Elan and Wyeth for the potential treatment of AD. AN1792 is a 42-amino acid long peptide mimicking amyloid beta. It induced the formation of antibodies against beta amyloid and was supposed to clear amyloid plaques from the brain of AD patients. However, the development of this vaccine had to be discontinued in March 2002 due to an inappropriate T-cell activation resulting in sterile encephalitis (companies' press releases of March 4, 2002). Although, immunization with synthetic amyloid beta (AN1792) cleared amyloid plaques in brain, this plaque clearance was not associated with improved cognition or survival in the long term (Holmes et al, 2008).

Two to four studies may be required to obtain a first insight into the compound's safety and tolerability as well as its potential efficacy. The main criteria to define efficacy are, as discussed earlier, cognition, activities of daily living and overall clinical response. As recommended in the revised "Guideline on Medicinal Products for the Treatment of Alzheimer's Disease and Other Dementias" (CPMP/EWP/553/95 Rev.1, see chapter 4.1.2) the following instruments could be employed:

- ADAS-cog (cognition)
- ADL, IADL, DAD, ADCS-ADL (activities of daily living which corresponds to the functional endpoint)
- CDR, ADCS-CGI-C, CIBIC-plus (overall clinical response which corresponds to the global endpoint)

***Phase III (approximately 1.000 patients per trial)***

Two positive pivotal Phase III studies are required for approval. The Phase III studies should be double blind, placebo-controlled, parallel group studies which will need to be conducted in several countries and include AD patients well defined according to the target population (e.g. mild to moderate AD according to the diagnostic criteria defined in DSM-III-R and NINCDS-ADRDA). These studies should have a duration of approximately 18 months. An open-label follow-up period of 12 to 24 months should be considered.

According to the guidelines available, long-term efficacy studies are ethically no longer acceptable if the patient does not receive the standard of care concomitantly. Thus, the investigational product needs to be studied in Phase III in an add-on design.

As in Phase II trials, the two primary outcome measures should be from the cognitive domain and from the functional or global domain. Furthermore, for disease-modifying investigational products a suitable biomarker should be defined which can be correlated with the mode of action. To achieve a full claim of disease-modification the test compound must show in two Phase III trials statistically significant improvement of the biomarker as well as statistically significant improvement of the core symptoms of AD.

As apolipoprotein E4 is an unequivocal risk factor for late-onset AD (Jiang et al, 2008), it may be advisable to conduct separate clinical trials for ApoE4 positive and negative AD patients.

***Safety Assessment***

In general any safety assessment should be designed according to the recommendations given in the ICH E1 guideline (see table in chapter 4.1.2). Depending on the proposed mechanism of action of the investigational compound certain adverse effects may need more attention. Due to the geriatric patient population and the indication it is particularly important to monitor carefully any neurological, psychiatric and cardiovascular adverse effects.

***Risk Management Plan***

A risk management plan is defined in the Regulation EC/1901/2006 and in the Volume 9A as a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, and the assessment of the effectiveness of those interventions.

The description of a risk management system should be submitted in the form of an EU-Risk Management Plan (EU-RMP). This EU-RMP contains two parts, namely part I which describes the safety specifications of the medicinal product and the corresponding pharmacovigilance plan, and part II which evaluates the need for risk minimization activities. These activities are used to reduce the probability of an adverse reaction occurring or its severity should it occur.

# 8 Summary and Conclusion

Alzheimer's disease is a very complex disorder which was described by Alois Alzheimer more than 100 years ago (Alzheimer 1907). Although its underlying pathology is still not entirely clear, research has accumulated a wealth of information on different mechanisms that account for one or the other aspect of the disease. Milestones in AD research were for example the identification of beta amyloid (A-beta 42) as the main component of amyloid plaques in 1984 by Glenner and Wong. This insight resulted in the formulation of the Amyloid Cascade Hypothesis (Hardy and Allsop, 1991) which claims that the disturbed metabolism of APP is the initiating event in AD pathogenesis. Thus, an important target for the development of new treatment approaches was identified which is still the basis of many research projects. Another milestone was the discovery that the intracellular neurofibrillary tangles observed in the brain of AD patients were composed of abnormally hyperphosphorylated tau protein (Grundke-Iqbal et al. 1986). The regulation of tau phosphorylation and how this regulation may be influenced by beta-amyloid gave rise to many new questions. Likewise, the finding that the expression of inflammatory mediators is increased in post-mortem brains of patients suffering from AD opened an entire new research field.

Consequently, a lot of different mechanisms of action are studied (see chapter 3.2) and a large number of compounds are developed for the potential treatment of AD. Many of these are putatively disease-modifying (see Annex 10.1). Despite all these research activities, no clinical proof-of-concept could be obtained to date and none of the main targets suspected of playing a major role in the pathology of the disease, such as beta-amyloid, could be validated as a reliable biomarker.

The regulatory requirements in both Europe and the US are relatively clear. Furthermore, there are no great differences in the regulatory requirements that need to be fulfilled to gain approval for a new AD therapy. At least in the case of memantine, the EMEA distinguishes more stages of AD (see chapter 5.2.3) and is more flexible concerning the primary outcome measures. Although the EMEA recommends using a cognitive and a functional endpoint as primary efficacy measure, the Agency accepted also clinical trials with a functional and a global endpoint in the case of advanced AD. Contrary to the EMEA, the FDA only accepts clinical trials for the efficacy assessment if one of the two primary endpoints is from the cognitive domain, independent of the stage of AD to be claimed (see chapter 5.2).

Although the regulatory framework is well defined, it has become more difficult to obtain a marketing authorisation for a new medicinal product to treat AD because the hurdles to show efficacy are higher today. Symptomatic improvement needs to be demonstrated on top of standard of care treatment, namely AChE inhibitors and/or memantine. This applies particularly to potentially disease-modifying treatments as these additionally need to demonstrate a correlation between a prospectively defined biomarker and clinically meaningful improvement of the core symptoms of AD (see chapter 4).

However, the analysis of the failure and subsequent discontinuation of the two most advanced and supposedly disease-modifying anti-Alzheimer therapies, namely Alzhemed® and Flurizan® (see chapter 6.1 and 6.2, respectively), indicates that rather than the lack of regulatory guidance, the lack of relevant disease-specific targets was the cause of the disappointing results.

Clearly, the best regulatory guidance is not able to bridge a gap in the scientific understanding of a disease. Thus, further intensive research will be required to identify the actual cause of AD and achieve a long awaited break-through in the treatment of this devastating disease.

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# 10 Annex

## *10.1 Pipeline Analysis*

## Drug Discovery Programmes for Alzheimer's Disease

### 1.) Beta Amyloid Modulators

#### Unspecified or Mixed Targets

| Company | Remark |
|---|---|
| ALSP | Small-molecule, beta-amyloid peptide production-reducing, secretase inhibitors. |
| Medisyn Technologies / Mount Sinai School of Medicine | Beta amyloid inhibitors, using Medisyn's Forward Engineering technology. |
| Resverlogix | NexVas AD, a small molecule series of apolipoprotein A1 (ApoA1) gene expression stimulators and serum HDL cholesterol enhancers. |
| Scripps Research Institute | Series of small molecule inhibitors of the constitutive mammalian protein transthyretin (TTR). |

#### Beta Secretase/BACE Inhibitors

| Company | Remark |
|---|---|
| Actelion | Series of BACE 1 inhibitors. |
| AstraZeneca/Astex | Series of BACE 1 inhibitors. |
| Bristol-Myers Squibb Co | Series of BACE 1 inhibitors. |
| Elan Corp plc | Series of small-molecule inhibitors of beta-secretase (BACE) |
| Eli Lilly & Co | Series of BACE 1 inhibitors. |
| Evotec | Series of BACE inhibitors, as part of its fragment based drug discovery platform. |
| GlaxoSmithKline plc | Series of BACE 1 inhibitors. |
| Johnson & Johnson | Series of BACE 1 inhibitors. |
| Kyoto University | Substrate-based beta-secretase inhibitors (BACE-1). |
| Medivir | Series of BACE 1 inhibitors. |
| Merck & Co / Sunesis | oral inhibitors of beta-secretase (BACE-1) |
| Novartis | Series of beta-site amyloid precursor protein-cleaving enzyme 1 (BACE 1) inhibitors. |
| ProMediTech/LG Life Sciences | Series of BACE 1 inhibitors. |
| Schering Plough Corp | Series of BACE 1 inhibitors. |
| Senex Biotechnology Inc | Series of candidates that block aging cells from producing amyloid precursor protein, BACE1 and tissue transglutaminase (TGM2). |
| Wyeth | Series of BACE 1 and 2 inhibitors. |

**Gamma Secretase Inhibitors**

| Company | Remark |
|---|---|
| Brigham & Women's Hospital / Harvard Medical School | Series of notch-sparing gamma secretase inhibitors. |
| Cellzome Inc / Ortho McNeil | Series of gamma secretase modulators. |
| EnVivo Pharmaceuticals Inc | Series of gamma secretase modulators. |
| Merck & Co | Series of gamma secretase modulators including MRK-560, L-685458, L-852505, L-852631 and L-852646. |
| Schering Plough Corp | Series of gamma-secretase inhibitors including SCH-697466. |

**2.) Nicotinic Acetylcholine Receptor (nAChR) Agonists**

| Company | Remark |
|---|---|
| Abbott Laboratories | Series of nicotinic acetylcholine receptor (nAChR) ligands, which lack the CNS or cardiovascular side effects. |
| Galanteos Pharma | Series of anti-apoptotic, nicotinic acetyl choline receptor (nAChR) allosteric potentiating ligands (APLs). |
| Wyeth / Siena Biotech | Small-molecule nicotinic acetylcholine receptor (nAChR) alpha 7 agonists, including SEN-12333 (WAY-317538). |

**3.) Muscarinic Receptor Modulators**

| Company | Remark |
|---|---|
| Acadia Pharmaceuticals | Series of muscarinic M1 agonists. |
| Eli Lilly | Series of muscarinic M1 agonists. |
| Vertex Pharmaceuticals | Series of M1 and M4-specific muscarinic receptor agonists, including VRTX-3. |

**4.) Others**

| Company | Remark |
|---|---|
| Ablynx / Boehringer Ingelheim | Series of injectable 'nanobodies', therapeutics derived from the naturally-occurring single chain antibodies of Camelidae. |
| Acumen Pharmaceuticals Inc / Merck & Co | Series of antibodies against amyloid-derived diffusible ligand (ADDL). |
| AstraZeneca | Series of glycogen synthase kinase-3 (GSK-3) inhibitors, including SN-2127, SN-3728, AR-014418 and AR-025028. |
| Circadian | Series of inhibitors to the p75 nerve growth factor receptor. |
| Cognosci | Series of apolipoprotein E-derived peptides. |
| Memory Pharmaceuticals | Series of PDE 4 inhibitors. |
| NeuroMolecular | Series of memantine (qv) derivatives which antagonize NMDA glutamate receptors and release nitric |
| Neuronascent Inc | Orally active compounds (nootropic agents) that stimulate neuron formation. |
| Northwestern University / NeuroMedix | Series of aminopyridazine-based, anti-neuroinflammatory candidates, known as Minozac. |
| OLIGOMERIX Inc | Series of compounds active against tau oligomers. |
| Palumed | Series of amyloid plaque production-inhibiting copper chelating agents. |
| Prana Biotechnology | PBT-3, a series of neuroprotective non-8-hydroxyquinoline compounds as a follow up to the PBT-2 series. |
| Probiodrug AG | Series of inhibitors of human glutaminyl cyclase (QC), which is thought to be involved in amyloid plaque formation. |
| Rottapharm SpA | Series of dual NMDA receptor antagonists and IL-6 inhibitors. |
| Samaritan Pharmaceuticals | Non-embryonic neuronal stem cell differentiation therapy drugs, including the naturally occurring compounds SP-sc4 and SP-sc7. |

## Drug Development Projects for Alzheimer's Disease

### 1.) Amyloid Synthesis Inhibitors:

#### Unspecified or Mixed Targets

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| AAD-2004 | Neurotech Pharmaceuticals Inc (Korea) / AmKor | Alzheimers disease, Dementia | Reduction of reactive oxygen species (ROS) and amyloid beta production. |
| EHT-0206 | ExonHit Therapeutics SA | Alzheimers disease | Orally-available small-molecule Rac1 GTPase inhibitor that can cross the blood-brain barrier and inderectly inhibits gamma secretase. |
| EHT-1864 | ExonHit Therapeutics SA | Alzheimers disease | RAC1 GTPase inhibitor |
| NG-2006 | Neurotech Pharmaceuticals Inc (Korea) / AmKor | Gastrointestinal disease, Alzheimers disease | Antioxidative, anti-inflammatory amyloid beta inhibitor analog of AAD-2004. |
| RGX-100 | RemeGenix Inc | Alzheimers disease | BRI2-derived peptide. |
| | | ***Phase I*** | |
| FGLL | ENKAM Pharmaceuticals | Alzheimers disease | Intranasal peptide NCAM (neural cell adhesion molecule) mimetic. |

#### Beta Secretase/BACE Inhibitors

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| ARC-050 | Archer Pharmaceuticals | Alzheimers disease | Beta secretase inhibitor |
| Posiphen | National Institutes of Health / Cenomed BioSciences | Drug-induced neurotoxicity, Alzheimers disease | (+)-enantiomer of phenserine. Filing of an IND application with the FDA planned for the end of 2008. |
| TTP-854 | TransTech Pharma Inc | Alzheimers disease | Beta-secretase-1 (BACE-1) inhibitor. |
| | | ***Phase I*** | |
| CTS-21166 | Zapaq Inc / Astellas Pharma | Alzheimers disease | Active peptide beta secretase inhibitors (oral and iv). |

**Gamma Secretase Inhibitors**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| ARC-069 | Archer Pharmaceuticals | Alzheimers disease | Gamma secretase subunit inhibitor |
| CHF-5074 | Chiesi Farmaceutici SpA | Alzheimers disease | Gamma secretase subunit inhibitor |
| NGX-555 | TorreyPines Therapeutics Inc (formerly Neurogenetics) | Alzheimers disease | In September 2008, the company was seeking to outlicense the project. |
| | | ***Phase I*** | |
| begacestat (GSI-953) | Wyeth | Alzheimers disease | Inhibitor of the aspartyl protease complex gamma-secretase (GSIs). |
| BMS-708163 | Bristol-Myers Squibb Co | Alzheimers disease | |
| E-2012 | Eisai Co Ltd | Alzheimers disease | |
| ELND-006 | Elan Pharmaceuticals Inc | Alzheimers disease | Gamma secretase subunit inhibitor. |
| GSI-136 | Wyeth | Alzheimers disease | By March 2008, two phase I trials of GSI-136 had been initiated. |
| MK-0752 | Merck & Co Inc | Alzheimers disease, T-cell acute lymphoblastic leukemia, Breast tumor, Cancer | Once-daily oral gamma secretase inhibitor and notch signalling pathway inhibitor. |
| PF-3084014 | Pfizer Inc | Alzheimers disease, Cancer | By December 2006, phase I trials for AD had begun. |
| | | ***Phase II*** | |
| NIC5-15 | Mount Sinai School of Medicine / Humanetics | Alzheimers disease | Orally active, natural antidiabetic compound which inhibits the formation of beta amyloid plaques and gamma-secretase. |
| | | ***Phase III*** | |
| semagacestat (LY-450139) | Eli Lilly & Co | Alzheimers disease | Gamma secretase subunit inhibitor. |

**2.) Beta Amyloid Aggregation/Deposition Inhibitors**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| AAB-002 | Elan Corp plc / Wyeth | Alzheimers disease | Monoclonal antibody. IND filed 03/2008 |
| ACI-01-Ab7 | AC Immune SA / Genentech | Alzheimers disease | Conformation-specific, passive immunotherapy with a selected anti-beta-amyloid monoclonal antibody. |
| AGT-160 | ArmaGen Technologies Inc | Alzheimers disease | Genetically engineered large molecule beta amyloid plaque formation inhibitor. |
| BAN-2203 | Bioarctic Neuroscience AB | Alzheimers disease | Second-generation immunotherapeutic that targets large soluble amyloid product (LSAP). |
| BAN-2401 | Bioarctic Neuroscience AB | Alzheimers disease | Humanized monoclonal antibody (mAb) that targets large soluble amyloid product (LSAP). |
| BGC-20-0406 | Senexis / BTG / Sankyo | Alzheimers disease | AKT protein kinase modulator that breaks the beta sheet formation. |
| DBTA-1339 | Digital Biotech Co Ltd | Alzheimers disease | Amyloid protein deposition inhibitor |
| INN-01 | Immuno-Biological Laboratories Co Ltd | Alzheimers disease | Beta-amyloid-specific humanized monoclonal antibody. |
| MPI-442691 | Mayo Foundation / Myriad Genetics | Alzheimers disease | Amyloid protein deposition inhibitor. |
| NHT-0112 | Neuro-Hitech Inc | Alzheimers disease | Second-generation compound that blocks the aggregation of beta-amyloid and tau-proteins. |
| NRM-8499 | Neurochem / Bellus Health Inc | Alzheimers disease | Prodrug of tramiprosate (3-amino-1-propanesulfonic acid). |
| PeptiClere | ProteoTech Inc | Alzheimers disease | Small peptide intranasal spray. |
| SDGII-T200801 | Bioalvo | Alzheimers disease | TAU/beta amyloid-targeting compound. |
| SEN-1329 | Senexis Ltd | Alzheimers disease | Small molecule aggregation inhibitor. |
| SP-233 (Caprospinol) | Georgetown University / Samaritan Pharmaceuticals | Spinal cord injury, Alzheimers disease, Parkinsons disease, Dementia | Small-molecule beta-amyloid binding, spirostenol drug. |
| SPI-014 | Satori Pharmaceuticals Inc | Alzheimers disease | |
| TKP-1001 | The Open University / EUSA Pharma | Alzheimers disease | Neuroprotective amyloid precursor protein (APP) fragment peptide mimetic. |
| VIP-SSM | University of Illinois | Alzheimers disease | Phospholipid nanomicelles containing vasoactive intestinal peptide (VIP) that prevent amyloid beta aggregation. |

| Drug | Company | Indication | Remark |
|---|---|---|---|
| ***Preclinical (continued)*** | | | |
| VK-12 | Prana Biotechnology Ltd | Alzheimers disease, Parkinsons disease, Cancer | Metallocomplex binding to the metal binding site on Abeta preventing other metals binding and causing structural corruption of Abeta. |
| ***Phase I*** | | | |
| ARC-031, ARC-031-SR | Archer Pharmaceuticals | Alzheimers disease | Non-calcium channel blocking and soluble amyloid reducing nilvadipine derivative. Additionally, a sustained release formulation is in development. |
| Exebryl-1 | ProteoTech Inc | Alzheimers disease | Synthetic analog of one of the components from an extract from the Amazonian vine Uncaria tomentosa. |
| HuCAL MAbs | Roche AG | Alzheimers disease | Human anti-beta amyloid monoclonal antibodies isolated using MorphoSys AG's HuCAL technology. |
| ***Phase II*** | | | |
| AZD-103 (ELND-005) | Transition / Elan | Alzheimers disease | Scyllo-cyclohexanehexol, an orally available, small-molecule inhibitor of amyloid beta aggregation. |
| ARC-029 | Roskamp Institute / Archer Pharmaceuticals | Alzheimers disease | Blood-brain-barrier crossing formulation of nilvadipine, a soluble amyloid reducing agent. |
| m266 | Eli Lilly & Co | Alzheimers disease | Antibody specific for the central domain of beta-amyloid. |
| PF-4360365 | Rinat Neuroscience Corp / Pfizer | Spinal cord injury, Alzheimers disease, Parkinsons disease | Humanized monoclonal antibody against amyloid beta. |
| solanezumab | Eli Lilly & Co | Alzheimers disease | Mid-domain humanized monoclonal antibody selective for soluble beta amyloid. Phase III is planned for 2009. |
| ***Phase III*** | | | |
| bapineuzumab | Elan Corp plc / Wyeth | Alzheimers disease | Humanized monoclonal antibody to amyloid beta. |

**3.) Chelating Agents**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| DP-460 | D-Pharm Ltd | Alzheimers disease, Motor neurone disease | Membrane active chelator (MAC) derivative of the calcium-specific chelator BAPTA. |
| M-30 | Weizmann Institute of Science / Technion | Alzheimers disease, Parkinsons disease | Combination of iron-chelating and monoamine oxidase (MAO) inhibitor activity. |
| PAN-811 | Panacea Pharmaceuticals Inc | Alzheimers disease, Ischemia | Ribonucleotide reductase inhibitor, which chelate calcium ions and scavenge free radicals. |
| Phanquinone | PN Gerolymatos SA | Alzheimers disease | |
| | | ***Phase II*** | |
| Gero-46 | PN Gerolymatos SA | Alzheimers disease | Copper chelating agent. |
| | | ***Phase III*** | |
| tetrathiomolybdate (Coprexa) | University of Michigan / Adeona Pharmaceuticals | Alzheimers disease, Huntingtons chorea, Wilson disease, Biliary tract disease, Pulmonary fibrosis | Copper chelating agent. For AD in phase II. |

**4.) Acetylcholineesterase (AChE) Modulators**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| bis-(7)-tacrine | Hong Kong University of Science & Technology | Alzheimers disease | bis-THA, bis-(12)-huperine, the dimeric derivative of tacrine. |
| donepezil | APR Applied Pharma Research SA | Alzheimers disease | Fast-dissolving oral film strip formulation. |
| donepezil | Eisai Co Ltd / Nitto Denko | Alzheimers disease | Transdermal formulation. |
| Memoquin | Universita di Bologna / Lay Line Genomics (LLG) | Alzheimers disease | AChE inhibitor, which is an agonist at the M2 presynaptic muscarinic receptor and blocks the aggregation of amyloid-beta. |
| rivastigmine | SCOLR Pharma Inc | Alzheimers disease | 24-h, oral, sustained-release tablet formulation. |
| SP-004 | Samaritan Pharmaceuticals | Alzheimers disease, Poison intoxication | Inhibitor of the sigma-1 receptor and acetylcholinesterase. |
| XEL-001HG | Xel Pharmaceuticals Inc | Alzheimers disease | Topical gel formulation of huperzine A. |
| | | ***Phase I*** | |
| BGC-20-1259 | Sankyo Co Ltd | Alzheimers disease | L-type calcium channel blocker, acetylcholinesterase (AChE) and 5-HT uptake inhibitor. Phase II trials were expected in 2008. |
| donepezil | Eisai Co Ltd | Alzheimers disease | Oral jelly formulation. |
| huperzine A | Neuro-Hitech Inc | Alzheimers disease | Transdermal patch. |
| NP-61 | Noscira SA | Alzheimers disease | Dual binding site acetylcholinesterase inhibitor. Positive phase I results were reported in November 2008. |
| | | ***Phase II*** | |
| huperzine A | Mayo Foundation / Neuro-Hitech | Alzheimers disease | Oral synthetic version of huperzine A. |
| mimopezil (DEBIO-9902) | Debiopharm / Shanghai Institute of Materia Medica of the Chinese Academy of Sciences | Alzheimers disease | Once-daily prodrug of huperzine A. Debiopharm is also developing a sustained release formulation. |

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Phase III*** | |
| Dimebon | Medivation Inc / Pfizer | Alzheimers disease, Huntingtons chorea | gamma carboline derivative. Orally active cholinesterase and NMDA receptor binding agent. |
| donepezil (Aricept) | Eisai Co Ltd | Alzheimers disease | Sustained release formulation. |
| | | ***Preregistration*** | |
| INM-176 | Scigenic & Scigen Harvest Co Ltd / WhanIn | Alzheimers disease | Natural product. |

**5.) Nicotinic Acetylcholine Receptor (nAChR) Agonists**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| Memogain (GLN-1062) | Galantos Pharma GmbH | Alzheimers disease | Clinical trials are expected to begin in 2009. |
| W56203 | Mitsubishi Pharma Corp | Alzheimers disease, Schizophrenia | Small-molecule alpha-7 nicotinic acetylcholine (ACh) receptor agonist. |
| | | ***Phase I*** | |
| EVP-6124 | Bayer AG / EnVivo | Alzheimers disease ; Schizophrenia | Phase II trials expected for 2009. |
| MEM-63908 | Memory Pharmaceuticals | Alzheimers disease, Central nervous system disease | Positive phase I results were published in December 2008. |
| | | ***Phase II*** | |
| AZD-0328 (ispronicline) | AstraZeneca plc | Alzheimers disease, Schizophrenia, Cognitive disorder | Nicotinic ACh receptor alpha 7 subunit stimulator. |
| MEM-3454 | Memory Pharmaceuticals / Roche | Alzheimers disease, Schizophrenia, Cognitive disorder, CNS disease | Nicotinic alpha-7 partial agonist/5-HT3 receptor antagonist. |
| pozanicline (ABT-089) | Abbott Laboratories | Alzheimers disease, Schizophrenia, ADHD | Nicotinic ACh receptor alpha 4 and beta 2 subunit stimulator. |
| SSR-180711 | Sanofi-Aventis | Alzheimers disease, Neurodegenerative disease, Schizophrenia, Cognitive disorder | |

**6.) Muscarinic Receptor Modulators**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| ANAVEX-1-41 | Anavex Life Sciences Corp | Alzheimers disease | Aminotetrahydrofuran derivative, a modulator of muscarinic and sigma-1 receptors as well as sodium and chloride channels. |
| | | ***Phase I*** | |
| MCD-386 | University of Toledo / Mithridion | Alzheimers disease | Small molecule second-generation tetrahydropyrimidine muscarinic M1 agonist. |
| | | ***Phase II*** | |
| NGX-267 | Life Science Research Israel | Xerostomia, Alzheimers disease, Schizophrenia | Muscarinic M1 receptor agonist |
| PYM-50028 | Phytopharm plc | Alzheimers disease, Parkinsons disease | Muscarinic M1 receptor modulator. |

**7.) NMDA Receptor Modulators**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| ANAVEX-2-73 | Anavex Life Sciences | Epilepsy, Alzheimers disease, Brain ischemia | Tetrahydrofuranic compound. |
| D-serine | Biovail / Glytech Inc | Alzheimers disease, Schizophrenia, Autism | Co-agonist at the NMDA receptor. |
| | | ***Phase II*** | |
| neramexane | Merz & Co GmbH | Alcoholism, Alzheimers disease, Pain, Parkinsons disease, CNS disease | |

**8.) 5HT Receptor Modulators**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| AP-267 | AcurePharma | Alzheimers disease, Acute stress disorder, Opiate dependence | Serotonin 5-HT2c receptor-modulating compound. |
| AV-965 | Avera Pharmaceuticals | Alzheimers disease | 5HT1a antagonist. |
| AVN-101 | Avineuro Pharmaceuticals Inc / ChemDiv Inc | Alzheimers disease | 5-HT 6 receptor antagonist. Clinical trials planned for 2009. |
| AVN-211 | Avineuro Pharmaceuticals Inc / ChemDiv Inc | Alzheimers disease ; Obesity | 5-HT 6 receptor antagonist. Clinical trials planned for 2009. |
| CD-0080045 | ChemDiv Inc | Alzheimers disease | 5-HT 6 receptor antagonist. |
| | | ***Phase I*** | |
| RQ-00000009 | Pfizer Inc | Alzheimers disease | 5-HT 4 receptor partial agonist. |
| SRA-444 | Wyeth | Alzheimers disease | 5-HT 1a receptor antagonist. |
| SUVN-502 | Suven Life Sciences Ltd | Alzheimers disease, Neurological disease | 5-HT 6 receptor antagonist. |
| | | ***Phase II*** | |
| PRX-03140 | Predix Pharmaceuticals Inc | Alzheimers disease, Cognitive disorder | 5-HT 4 receptor agonist. |
| SAM-531 | Wyeth | Alzheimers disease | 5-HT 6 receptor antagonist. |
| SB-742457 | GlaxoSmithKline plc | Alzheimers disease, Schizophrenia | 5-HT 6 receptor antagonist. |

**9.) Ion Channel Modulators**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| NP-17 | Noscira SA | Alzheimers disease | Calcium channel blocking and AChE inhibiting compound derived from the marine sponge Aplysina cavernicola. |
| SPI-017 | Sucampo Group | Alzheimers disease | Oral formulation of an iv prostone drug. Phase I trials were to start in 2009. |
| | | ***Phase II*** | |
| MEM-1003 | Bayer AG / Memory Pharmaceuticals | Alzheimers disease, Mania, Neurodegenerative disease, Cognitive disorder, CNS disease, Bipolar disorder, Dementia | Oral, neuronal L-type calcium channel blocker. |

**10.) Phosphodiestease (PDE) 4 Inhibitors**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| DG-071 | deCODE genetics Inc | Alzheimers disease, Cognitive disorder | In October 2008, an IND was submitted. |
| MEM-1917 | Memory Pharmaceuticals | Alzheimers disease, Major depressive disorder | Back-up of MEM-1414. |
| | | ***Phase I*** | |
| AVE-8112 | sanofi-aventis | Alzheimers disease | |
| EHT-0202 | ExonHit Therapeutics SA | Alzheimers disease, Neurodegenerative disease | Oral small-molecule PDE4 inhibitor and GABA-A modulator. |
| | | ***Phase II*** | |
| MEM-1414 | Memory Pharmaceuticals | Alzheimers disease | |

**11.) Vaccines**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| ACI-24 | AC Immune SA | Alzheimers disease | Liposome-based conformation-specific vaccine to target the N-terminus of the amyloid-beta (A-beta) peptide. |
| AdPEDI (Abeta1-6)11 | Vaxin Inc | Alzheimers disease | Vaccine, amyloid protein deposition inhibitor. |
| Alzheimer's disease vaccines | University of South Florida / University of New Mexico | Alzheimers disease | Amyloid beta peptides conjugated to a bacteriophage. |
| beta amyloid vaccine | University of California Irvine / Kinexis | Alzheimers disease | Beta amyloid soluble oligomer vaccine. |
| DNA vaccine | DNAVEC Corp | Alzheimers disease | Intranasal vaccine comprising a Sendai virus vector encoding the amyloid beta gene. |
| immunotherapy | Prana Biotechnology Ltd | Alzheimers disease | Monoclonal antibody vaccine, that targets pathological oxidated amyloid beta oligomers. |
| peptide vaccine | Hayashibara Biochemical Laboratories Inc | Alzheimers disease | Transmucosal formulation. |
| PEVIPRO | Pevion Biotech AG | Alzheimers disease | Virosomes that have beta amyloid peptide antigen linked to the surface. |
| RECALL-VAX | Intellect Neurosciences Inc | Alzheimers disease | Chimeric peptide vaccine combining a short fragment of beta-amyloid with part of the tetanus toxoid. |
| | | ***Phase I*** | |
| Affitope AD-01 | AFFiRiS GmbH / GSK | Alzheimers disease | Peptide-based vaccine based on proprietary Affitome technology. Phase I initiated in July 2007. |
| Affitope AD-02 | AFFiRiS GmbH / GSK | Alzheimers disease | Peptide-based vaccine based on proprietary Affitome technology. Phase I initiated in February 2008. |
| V-950 | Merck & Co Inc | Alzheimers disease | Anti-amyloid beta (A-beta) vaccine. |
| | | ***Phase II*** | |
| ACC-001 | Elan Corp plc / Wyeth | Alzheimers disease | Peptide fragment of amyloid beta conjugated to CRM. |
| ACC-002 | Elan Corp plc / Wyeth | Alzheimers disease | Peptide fragment of amyloid beta conjugated to CRM. |
| CAD-106 | Cytos Biotechnology AG / Novartis | Alzheimers disease | Beta amyloid modulator. |

**12.) Others**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical*** | |
| ADNF-14 | National Institutes of Health | Alzheimers disease | Neuroprotectant, activity-dependent neurotropic factor-14. |
| AFX-929 | Afecta Pharmaceuticals | Alzheimers disease | Nootropic agent |
| beta NGF | Apollo Life Sciences Pty Ltd | Alzheimers disease | Beta NGF tethered to a molecular shuttle. |
| bisnorcymserine | Axonyx Inc | Alzheimers disease, drug-induced Neurotoxicity | Dual butyrylcholinesterase (BChE) and beta-amyloid precursor protein (APP) inhibitor. |
| ciproxifan | INSERM | Epilepsy, Alzheimers disease, Dementia | Histamine H3 receptor antagonist. |
| CX-1501 | Cortex Pharmaceuticals Inc | Alzheimers disease, Sleep disorder, ADHD | AMPA receptor modulator |
| CX-1796 | Cortex Pharmaceuticals Inc | Alzheimers disease, ADHD, Respiratory disorder | Low impact AMPAKINE compound, AMPA receptor modulator. |
| CX-717 | Cortex Pharmaceuticals Inc | Alzheimers disease, ADHD, Respiratory disorder | iv formulation, an AMPA receptor modulating AMPAKINE compound. |
| CNP-1061 | Cita NeuroPharmaceuticals Inc | Alzheimers disease, Seizure disorder | NO modulator |
| colivelin | Neurologix / Keio University | Alzheimers disease, Motor neurone disease | Hybrid peptide composed of activity-dependent neurotrophic factor (ADNF) and a humanin derivative (gene therapy). |
| cystatin C | New York University / Nathan Kline Institute | Alzheimers disease | Cysteine protease inhibitor. |
| EHT-0205 | ExonHit Therapeutics SA | Alzheimers disease, Vascular dementia | Histone deacetylase (HDAC) inhibitor. |
| galanin antagonists | Lundbeck Research USA Inc | Endocrine disease, Alzheimers disease, Pain, Obesity, Major depressive disorder | |
| LLG-88 | Lay Line Genomics SpA | Alzheimers disease | Intranasal formulation of nerve growth factor (NGF). |
| MAP-4343 | Mapreg | Spinal cord injury, Alzheimers disease | Microtubule associated protein 2 stimulator. In March 2008, the drug was granted EU Orphan Drug status for SCI. A phase I trial was expected to begin towards the end of 2008. |
| MDA-200C | Medeia Therapeutics Ltd | Alzheimers disease | Cell-based therapy. |
| MW01-5-188WH | Northwestern University / Neuromedix | Alzheimers disease | Orally-active and suppressor of upstream proinflammatory cytokine production by activated glia. |

| Drug | Company | Indication | Remark |
|---|---|---|---|
| | | ***Preclinical (continued)*** | |
| NC-1900 | Nippon Chemiphar Co Ltd / DelSite | Alzheimers disease | Vasopressin receptor modulator. Intranasal powder formulation of NC-1900, an arginine vasopressin metabolite. |
| Neu-2072 | Neurotech Pharmaceuticals Inc (Korea) | Gastrointestinal disease, Alzheimers disease, Parkinsons disease | Antioxidant free radical scavengers which attenuate zinc ion entry. |
| NGN-9079 | NeuroGeneration Inc | Alzheimers disease | Neural stem cell therapy. |
| NP-103 | Noscira SA | Alzheimers disease | Glycogen synthase kinase-3 inhibitor. |
| NP-901 | Noscira SA | Alzheimers disease | Trophic factor. |
| NT-69-L | Mayo Foundation | Alzheimers disease, Pain, Schizophrenia, Nicotine dependence, Parkinsons disease, Cognitive disorder | Neurotensin (NT) hexapeptide. |
| PNB-04 | PharmaNeuroBoost NV | Alzheimers disease | Neuroprotectant. Phase I was planned for 2008. |
| ReN-004 | ReNeuron (UK) Ltd | Alzheimers disease, Parkinsons disease | Neural stem cell therapy. |
| ReS19-T | reMYND NV | Alzheimers disease | Neuroprotectant. Phase I was planned for 2008. |
| RGX-200 | RemeGenix Inc | Alzheimers disease | Nootropic agent. |
| RTA-404 | Reata Pharmaceuticals Inc | Alzheimers disease, Multiple sclerosis, Parkinsons disease, Brain tumor | Unspecified cytokine receptor antagonist. |
| SEN-1176 | Senexis Ltd | Alzheimers disease | Small molecule neuroinflammation inhibitor. |
| SOD1 | Amorfix Life Sciences Ltd | Alzheimers disease ; Motor neurone disease | Superoxide dismutase modulator |
| TTP-4000 | TransTech Pharma Inc / Pfizer | Diabetic nephropathy, Alzheimers disease | Advanced glycosylation product receptor modulator (RAGE). |
| UC-1011 | Umecrine AB | Alzheimers disease | GABA A receptor antagonist. |
| ZSET-1446 | Zenyaku Kogyo Co Ltd | Alzheimers disease, Cognitive disorder, Major depressive disorder | Nootropic agent. |
| | | ***Phase I*** | |
| aleplasinin (PAZ-417) | Wyeth | Alzheimers disease | Plasminogen activator inhibitor (PAI) inhibitors. |
| ASP-2535 and ASP-2905 | Astellas Pharma Inc | Alzheimers disease, Schizophrenia | Undisclosed mechanism. |
| CERE-110 | Ceregene Inc | Alzheimers disease | Adeno-associated virus vector based gene therapy. Stereotaxic injection of fibroblasts transfected with nerve growth factor.Phase II expected in 2009. |

| Drug | Company | Indication | Remark |
|---|---|---|---|
| ***Phase I (continued)*** | | | |
| davunetide (AL-208) | Allon Therapeutics Inc | Alzheimers disease, Brain ischemia, Neurodegenerative disease, Cognitive disorder | sc formulation of the eight-amino acid peptide derived from activity-dependent neuroprotective protein. |
| ECT-AD | NsGene A/S | Alzheimers disease | Encapsulated cell technology (ECT) to deliver cells expressing NGF. |
| GSK-933776A | GlaxoSmithKline plc | Alzheimers disease | Monoclonal antibody. Undisclosed target. |
| MABT-5012A | Genentech Inc | Alzheimers disease | In August 2008, a phase I trial was initiated. |
| NEBO-178 | Stegram Pharmaceuticals Ltd / Neuro Bioscience | Alzheimers disease | Sigma receptor antagonist that increases estrogen binding to ERbeta in the memory center of the brain and increases dehydroepiandrosterone (DHEA) levels. |
| NP-12 | Noscira SA | Alzheimers disease, Central nervous system disease | Tau kinase inhibitor, Glycogen synthase kinase-3 beta inhibitor. Phase II trials were expected for end of 2008. |
| OXIGON | Intellect Neurosciences / New York University | Alzheimers disease, Huntingtons chorea, Parkinsons disease | An antioxidant and anti-amyloid compound. Phase II studies are expected in 2009. |
| Protexia | Nexia Biotechnologies Inc / PharmAthene | Alzheimers disease, Toxicity | Cholinesterase stimulator. Recombinant human butyrylcholinesterase produced in the milk of transgenic goats, in a PEGylated formulation. |
| TAK-065 | Takeda Pharmaceutical | Alzheimers disease, Parkinsons disease | Oral neuroregeneration enhancer. |
| ***Phase II*** | | | |
| CX-717 | Cortex Pharmaceuticals Inc | Alzheimers disease, ADHD, Respiratory disorder | Oral formulation, an AMPA receptor modulating AMPAKINE compound. |
| davunetide (AL-108) | Allon Therapeutics Inc | Alzheimers disease, Brain ischemia, Neurodegenerative disease, Cognitive disorder | Intranasal spray formulation of the eight-amino acid peptide derived from activity-dependent neuroprotective protein. |
| EVT-302 | Roche Holding AG | Alzheimers disease, Nicotine dependence | MAO B inhibitor. |
| HF-0220 | Hunter-Fleming Ltd / Newron Pharmaceuticals | Alzheimers disease, Inflammatory disease, Neurodegenerative disease, Rheumatoid arthritis, Ischemia | Prostaglandin D synthase stimulator. |
| LY-451395 | Eli Lilly & Co | Alzheimers disease, Neurodegenerative disease | AMPA receptor agonist. |
| MK-0249 | Merck & Co Inc | Alzheimers disease, Sleep apnea, Psychiatric disorder, Schizophrenia, ADHD | Undisclosed mechanism. |

| Drug | Company | Indication | Remark |
|---|---|---|---|
| ***Phase II (continued)*** | | | |
| ONO-2506PO (Cereact) | Ono Pharmaceutical Co Ltd | Alzheimers disease, Motor neurone disease, Neurodegenerative disease, Parkinsons disease | Oral capsule formulation of arundic acid, a neurotropic agent that modulates astrocyte function. |
| PBT-2 | Prana Biotechnology Ltd | Alzheimers disease, Huntingtons chorea | Orally active tau hyperphosphorylation inhibitor, synthetic amyloid beta inhibitor and metal-protein attenuating compound (MPAC). |
| PF-3654746 | Pfizer Inc | Allergic rhinitis, Alzheimers disease, Schizophrenia, ADHD, Cognitive disorder | Histamine H3 receptor antagonist. |
| PF-4494700 | TransTech Pharma Inc / Pfizer | Diabetic nephropathy, Alzheimers disease | Advanced glycosylation product receptor modulator (RAGE). |
| T-817MA | Toyama Chemical Co Ltd | Alzheimers disease | Neurotrophic benzothiophene derivative. |
| ***Phase III*** | | | |
| EGb-761 (Tanakan) | Dr Willmar Schwabe GmbH & Co | Alzheimers disease, Parkinsons disease, Neurological disease | Free radical scavenger, Ginkgo biloba extract. |
| leuprolide acetate implant (Memryte) | Voyager Pharmaceutical Corp | Alzheimers disease | GNRH agonist, biodegradable implant formulation. |
| rosiglitazone XR | GlaxoSmithKline plc | Alzheimers disease, Rheumatoid arthritis | Extended-release formulation of the PPAR gamma agonist. |

## Launched Products for Alzheimers Disease

### 1.) Acetylcholineesterase (AChE) Inhibitors

| Drug | Company | Indication | Remark |
|---|---|---|---|
| ***Launched*** | | | |
| donepezil (Aricept) | Eisai Co Ltd | Alzheimers disease, migraine, dementia | Acetylcholinesterase inhibitor. Widely launched for AD |
| donepezil | Eisai Co Ltd | Alzheimers disease | Acetylcholinesterase inhibitor, rapid oral disintegration tablet (RDT, ODT) |
| galantamine | Sanochemia Pharmazeutika AG | Postviral fatigue syndrome, Alzheimers disease, arthritis | Acetylcholinesterase inhibitor, extracted from daffodil bulbs. |
| galantamine (Razadyne ER, Reminyl XL) | Johnson & Johnson | Alzheimers disease | extended release capsule formulation of the acetylcholinesterase inhibitor galantamine |
| Huperzine A | Shanghai Institute of Materia Medica | Alzheimers disease | acetylcholinesterase (AChE) inhibitor. Launched only in China in 1995. |
| minaprine | sanofi-aventis | Major depressive disorder, Alzheimers disease | Acetylcholine release stimulator. Only launched in France and South Korea. |
| rivastigmine | Novartis AG | Alzheimers disease, cognitive disorder, dementia | Acetylcholinesterase inhibitor. Widely launched for AD. |
| tacrine | Warner-Lambert Co | Alzheimers disease | Acetylcholinesterase inhibitor with weak potassium channel antagonist properties. Launched widely. |

### 2.) NMDA Receptor Modulators

| Drug | Company | Indication | Remark |
|---|---|---|---|
| ***Launched*** | | | |
| memantine | Merz & Co GmbH | Neuropathic pain, glaucoma, Alzheimers disease, Binge eating disorder, ocular disease, ocular hypertension, dementia | NMDA receptor antagonist. Widely launched. |

**3.) Others**

| Drug | Company | Indication | Remark |
|---|---|---|---|
| ***Launched*** | | | |
| acetyl-L-carnitine hydrochloride (Nicetile, Zibren) | Sigma-Tau Ind Farm Riunite SpA | Diabetic neuropathy, Alzheimers disease, Psychiatric disorder, Peripheral neuropathy, Cerebral infarction, Fatigue, Dementia | Apoptosis inhibitor and memory enhancer. Launched for AD in Italy and South Korea. |
| idebenone | Takeda Pharmaceutical Co Ltd | Alzheimers disease, ataxia | oral brain energy metabolism enhancer, lipid peroxidation inhibitor and oxidoreductase inhibitor. Only launched in Portugal and Italy. Withdrawn from Japaneese market due to safety concerns. |
| mecobalamin | Eisai Co Ltd | Diabetic neuropathy, neuralgia, infertility, glaucoma, Alzheimers disease, urinary incontinence, leukemia, peripheral neuropathy, sleep disorder, genitourinary disease | vitamin B12 agonist. Widely launched. |
| moclobemide | Roche Holding AG | Alzheimers disease, anxiety disorder, psychosis, dementia, major depressive disorder | MAO-A inhibitor. Launched extensively as an antidepressant but only in Switzerland for AD. |
| oxiracetam | ISF Societa Per Azioni (subsidiary of Smithkline Beecham) | Alzheimers disease, dementia | Nootropic agent |

## *10.2 CPMP/EWP/553/95 (Revision 1) – Note for Guidance on Medicinal Products in the Treatment of Alzheimer's Disease*

European Medicines Agency
*Pre-Authorisation Evaluation of Medicines for Human Use*

London, 24 July 2008
Doc. Ref. CPMP/EWP/553/95 Rev. 1

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE**

**(CHMP)**

# GUIDELINE ON MEDICINAL PRODUCTS FOR THE TREATMENT OF ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

| | |
|---|---|
| **DRAFT AGREED BY THE EFFICACY WORKING PARTY** | June 2007 |
| **ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION** | 19 July 2007 |
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| **KEYWORDS** | *Alzheimer's Disease, Dementia, Dementia with Lewy Body Disease, Dementia with Parkinson's Disease, disease modifying treatment, prevention, symptomatic treatment, Vascular Dementia* |

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**GUIDELINE ON MEDICINAL PRODUCTS FOR THE TREATMENT OF ALZHEIMER'S DISEASE AND OTHER DEMENTIAS**

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## EXECUTIVE SUMMARY

The present document should be considered as general guidance on the development for medicinal products for the treatment of dementia and its subtypes, and should be read in conjunction with other EMEA and ICH guidelines, which may apply to these conditions and patient populations.

Based on efficacy and safety data several drugs have been approved for symptomatic improvement of dementia of the Alzheimer Type and one for the symptomatic improvement of dementia associated with Parkinson's Disease. However, established treatment effects must be considered as modest. Randomized clinical trials in other subtypes of dementia (e.g. vascular dementia) have not been able to demonstrate clinically relevant symptomatic improvement nor was it yet possible to establish disease modifying effects in any dementia syndrome or its subtypes. Recent progress in basic science and molecular biology of the dementias has now fostered new interest for more efficacious symptomatic treatments as well as for disease modifying approaches in the dementias.

For regulatory purposes this requires better standardization and refinement of diagnostic criteria, which allow the study of homogeneous disease populations in specialized academic centres as well as in the general community setting. Depending on the disease stages (early versus late, mild to moderate to severe impairment) and disease entities distinct assessment tools for cognitive, functional and global endpoints should be used or newly developed. The typical design to show symptomatic improvement is a randomized, double-blind, placebo-controlled, parallel group study comparing change in two primary endpoints, one of them reflecting the cognitive domain and the second preferably reflecting the functional domain of impairment. The changes must be robust and clinically meaningful in favour of active treatment versus placebo.

If a treatment claim for prevention of the emergence, slowing or stabilizing deterioration is strived for, it has to be shown that the treatment has an impact on the underlying neurobiology and pathophysiology of the dementing process. Establishing such an effect in a highly variable progressing syndrome is complex and difficult, however, a variety of trial designs has been provided including baseline designs, survival designs, randomized delayed-start or randomized withdrawal designs with or without incorporation of biomarkers (e.g. magnetic resonance tomography, emission tomography, cerebrospinal fluid markers). To be accepted as a surrogate endpoint such a biomarker should satisfy certain criteria including, though not limited to, responding to treatment, predicting clinical response and being compellingly related to the pathophysiological process of the dementing condition. However, careful and sufficient validation of the proposed biomarkers as a potential surrogate endpoint is a precondition for acceptance by regulatory bodies.

## 1. INTRODUCTION

The term dementia describes a syndrome characterised by memory impairment, intellectual deterioration, changes in personality and behavioural abnormalities (DSM-IV-TR, ICD-10). These symptoms are of significant severity to interfere with social activities and occupational functioning. Moreover, the observed cognitive deficits must represent a decline from a higher level of function. In general, the disorders constituting the dementia syndromes share a common symptom presentation and are identified and classified on the basis of different etiologic factors and separate pathophysiological pathways. However, distinct subtypes of dementia syndromes are identifiable based on etiologic factors, clinical presentation, and pattern of impairment, natural course of the dementia syndrome and laboratory or neuroimaging tools. Alzheimer's Disease (AD) is the most common cause of dementia, followed by vascular dementia (VaD) or mixed forms of Alzheimer's disease and vascular dementia (MIXD). Other forms of neurodegenerative disorders as Parkinson's disease (PD), Lewy-Body disease (LBD), Huntington's disease, fronto-temporal dementia and others are accompanied in a subset of patients with dementia as well. Thus based on these distinct aetiologies and clinical features there will be probably be no single "anti-dementia" drug, but different drugs should be developed directed towards either symptomatic change or to modification of aetiological and pathophysiological processes.

The main goals of treatment for dementia are:

- Symptomatic improvement, which may consist in enhanced cognition, more autonomy and/or improvement in neuropsychiatric and behavioural dysfunction.

- Disease modification with slowing or arrest of symptom progression of the dementing process.
- Primary prevention of disease by intervention in key pathogenic mechanisms at a pre-symptomatic stage.

It should be recognised that the treatment of AD and other dementias is still an open research field. For symptomatic treatment the development and use of reliable and sensitive instruments to measure cognition, functional and behavioural symptoms, particularly for the assessment of activities of daily living (ADL), and neuropsychiatric symptoms is encouraged.

Currently there is a lack of agreement on the appropriate methodology to demonstrate slowing or arrest of the dementing process and experience is mostly based on patients with Alzheimer's disease. Ideally proof of a disease modifying effect would require demonstration of clinically relevant changes in key symptoms of the dementia syndrome and in addition supportive evidence for change in the underlying disease process based on biological markers, e.g. neuroimaging marker as serial MRI of the hippocampal region or whole brain, which are under validation.

Data on prevention of dementing conditions are still very limited and have been disappointing up to now. Taking into consideration vascular dementia modification and control of the major risk factors for cardiovascular and cerebrovascular disorders has been shown effective in preliminary results from observational epidemiological studies. Another prevention strategy takes into account that several of the traditional cardiovascular risk factors are associated with AD as well. Prevention studies in dementia need to be large, may last for many years and due to that must take into consideration high drop out rates, may be partly due to these problems up to now no positive results are available for secondary prevention in dementing conditions. However, enrichment strategies and the development of better screening and measurement tools for asymptomatic or very mild forms of dementia combined with biomarkers may help to gain more data in the future.

## 2. SCOPE

The rapid increase of ageing populations with its accompanying set of chronic illnesses and the age-dependent exponential rise in the prevalence of dementia is recognized. In the last decades significant progress has been made in basic and clinical research in dementing conditions. Therefore the aim of this updated document is to provide guidance in the development of clinical studies for the treatment of dementia incorporating new research data and experience from recent clinical trials and development programs. The present document addresses not only Alzheimer's disease as the most common form of dementia, but should be applicable to other forms of dementia as vascular dementia, dementia associated with Parkinson's disease and Lewy Body Disorder, Huntington's disease or fronto-temporal dementia as well. Special emphasis is given to diagnostic criteria of these conditions and their implications for inclusion and exclusion criteria on the one hand, and to new assessment tools suitable as primary and secondary endpoints on the other hand. Recently in addition to symptomatic treatment new emphasis is given to possible disease modifying approaches. A lot of research focused on biomarkers as possible surrogate endpoints, however, yet none has been sufficiently qualified and validated. This together with new treatment options with distinct modes of action requires different study designs, which have to be adjusted for their particular conditions.
Qualification and validation of a certain biomarker as supportive evidence or as a surrogate endpoint is out of the scope of this guideline and may be outlined in detail in separate upcoming documents.

## 3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and part of the Annex I to Directive 2001/83/EC as amended and relevant CHMP Guidelines, among them:

- Dose-Response information to Support Drug Registration (CPMP/ICH/378/95 (ICH E4))
- Statistical Principles for Clinical Trials (CPMP/ICH/363/96 (ICH E9))
- Choice of Control Group in Clinical Trials (CPMP/ICH/364/96 (ICH E10))
- Adjustment for Baseline covariates (CPMP/EWP/2863/99)
- Points to Consider on Missing data (CPMP/EWP/177/99)

- Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)
- Choice of a Non-Inferiority Margin (CPMP/EWP/2158/99)
- Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95 (ICH E1A))
- Studies in support of special populations: geriatrics (CPMP/ICH/379/99 (ICH E7))
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A)
- Investigation of Drug Interactions (CPMP/EWP/560/95)
- Note for Guidance on the Clinical Evaluation of Vaccines **(C**HMP/VWP/164653/2005)
- Clinical Investigation of Medicinal Products in the Treatment of Parkinson's Disease (CPMP/EWP/563/95 Revision 1)

## 4. MAIN GUIDELINE TEXT

### 4.1 Diagnostic Criteria

#### *4.1.1 Diagnosis of dementia*

The clinical syndrome of dementia and the criteria for its severity are defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR of the American Psychiatric Association) and in ICD-10 (F00-F03) of the WHO. For the effective and consistent evaluation of patients with dementia a stable diagnostic framework must be followed.

According to these definitions, the diagnosis of dementia remains primarily clinical. It is based on a careful history, obtained from the patient and their relatives and care givers. The history should demonstrate a typical progressive deterioration of cognitive and non-cognitive functions and some functional and behavioural consequences of this deterioration. At neurological and neuropsychological examination, there must be explicit impairments in memory and other cognitive domains, in the absence of developmental deficits.

One particular shortcoming of these criteria is the strong focus on memory deficits, which is adequate for patients with Alzheimer’s disease, whereas dementia syndromes with differing aetiologies frequently may present without prominent memory impairment. The request of a progressive deterioration in any two cognitive domains resulting in impairment of social and occupational function may be more adequate, and needs to be established and further validated.

These impairments should not be explained by another major primary psychiatric disorder.

#### *4.1.2 Severity of dementia*

The DSM-IV-TR and ICD 10 incorporate criteria for mild, moderate and severe dementia. The degree of severity of dementia of the included patients should be assessed and the method used should be stated. Simple screening tests, such as the Mini Mental State Examination (MMSE), have been used to document the extent of cognitive dysfunction, e.g. mild to moderate versus severe impairment. Revised definitions should rely not only on the cognitive dimension, but also take into account levels of functional disability and neuropsychiatric symptoms. Outcome measures in very mild, mild to moderate or moderate to severe patient populations must be able to assess the stage specific symptoms, which are of clinical relevance. Therefore the severity of cognitive impairment and behavioural changes and the resulting changes in self-care and other activities of daily living (ADL) should be documented using a variety of specific and global rating instruments.

Yet no treatments for early intervention are available to prevent widespread and irreversible neuropathological changes. However, the emergence and the experience with terms like “mild cognitive impairment” have shown that it is necessary to develop more sensitive and specific diagnostic criteria for early disease, which at the same time are valid and reliable (see also Section 4.1.5). This and the shortcomings of the diagnostic term dementia as mentioned earlier fostered the development of research criteria for early Alzheimer’s disease, which are in the process of further validation.

#### *4.1.3 The diagnosis of Alzheimer's disease and other dementias*

*Alzheimer’s Disease*

The probability that a dementia syndrome is caused by AD is essentially based on a history of a steadily progressive course and on the absence of evidence for any other clinically diagnosable cause of the dementia. It can be further specified by using the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke; Alzheimer's Disease and Related Disorders Association). Knowledge about AD is accumulating rapidly, thus the diagnostic criteria used may need revision and updating (validation of new research criteria for early Alzheimer's disease adding information from biomarkers to memory deficits are underway). Whereas sensitivity has been shown very good to excellent, specificity has been much lower in many studies, and assessment of inter-rater reliability has shown high variability. Patients with brain biopsy proven definite AD are usually not available. Currently patients with probable AD according to the NINCDS-ADRDA criteria are the most appropriate group in whom to study the effects of drugs.

However, there are clear limitations of the NINCDS-ADRDA criteria to exclude patients with mixed AD-VaD or other dementia syndromes.

*Vascular and Mixed Dementia*

In clinical trials vascular dementia has traditionally been diagnosed by the Hachinski-Score and its modified versions or the criteria of the National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN). Similarly to the NINCDS-ADRDA criteria in AD the NINDS-AIREN criteria allow the distinction of possible and probable disease, they show high specificity but low sensitivity for vascular dementia. In some trials on vascular dementia the criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centres have been used as inclusion criteria, sensitivity using these criteria is high, however, specificity is lower. Independent of the criteria used for VaD inter-rater reliability is lower than in AD. So it is not surprising that in comparative studies different patient populations have been identified by the different criteria. For regulatory purposes therefore the NINDS-AIREN criteria with there high specificity are still preferred until better criteria are available.

A large proportion of patients with dementia shows evidence of multiple overlapping neuropathological processes with combination of neurodegenerative and vascular changes (30 to 40%). AD and VaD very often coexist and constitute the large group of patients with mixed dementia (MIXD). Up to now no consistent diagnostic framework has been established to distinguish these mixed forms of dementia from "pure" forms of vascular or Alzheimer's dementia. However, use of structural neuroimaging is standard in all dementia therapeutic trials and is considered as an essential part within the work-up of patients with dementia to allow determination of vascular elements in the differential diagnosis. Due to the large proportion of these patients in the dementia population treatment options should be available, therefore in clinical trials a specific diagnostic and assessment framework must be developed for these patients as efficacious treatments in "pure" AD or VaD cannot be extrapolated. It is recommended to start development in "pure" disease forms and thereafter extend the scope of development to the "mixed" forms.

*Dementia with Parkinson's Disease and Dementia with Lewy Bodies*

Based on recent research Parkinson Disease with Dementia (PDD) and dementia with Lewy bodies (DLB) are subsumed under the umbrella term "Lewy body disorders". However, based on the differing temporal sequence of key symptoms and clinical features of PDD and DLB distinction of these concise subtypes is still justified.

Patients with Parkinson's disease show an increased risk for dementia based on epidemiological studies. Based on systematic reviews patients with Parkinson's disease suffer from additional dementia in 24 to 31 % and 3 to 4 % of dementia burden is due to Parkinson's disease. Operationalised criteria for patients with PDD have been proposed recently, however data on sensitivity and specificity have not been fully established. A current pragmatic approach requires at least one year of major parkinsonian motor symptoms before the onset of symptoms of dementia.

The criteria by McKeith et al. have become a standard for studies in dementia with Lewy Bodies (DLB), which show a very high specificity but low sensitivity. Clinical core features of DLB consist of rapid fluctuations in cognition, recurrent visual hallucinations and spontaneous and fluctuating features of parkinsonism, these are further supported by high sensitivity for extrapyramidal side effects to neuroleptics and rapid eye movement sleep behaviour disorder.

*Fronto-temporal Dementia and others*

In a very preliminary stage for regulatory purposes are the criteria for fronto-temporal dementia and its subtypes. However, as fronto-temporal dementia probably is a prevalent cause of dementia, further validation of these criteria is needed.

Other rare conditions associated with dementia as Huntington's Disease can be diagnosed by detection of their genetic abnormality, e.g. "Huntingtin" can be reliably measured by a blood test, which allows confirmation or exclusion of Huntington's disease with great accuracy.

### *4.1.4 Selection criteria for Alzheimer's disease and other dementias*

As stated above, the diagnosis of AD and other dementias consists of three steps: first, the clinical diagnosis of dementia; second, the exclusion of other causes of dementia and third, diagnostic classification of the dementia subtype. This relies on a careful history with a clinical neurological examination and technical (e.g. brain imaging modalities using MRI or emission tomography based techniques) and laboratory methods (e.g. beta-amyloid, tau-protein, phospho-tau, proteomics in the cerebrospinal fluid). The latter is evolving rapidly and preliminary data show, that it may be possible to better define patient populations by distinguishing AD and other dementias with higher sensitivity and specificity. Other causes of dementia to be excluded with appropriate methods include in particular treatable causes of dementia as infections of the CNS (e.g. HIV, syphilis) or Creutzfeld-Jakob disease. Subdural haematoma, communicating hydrocephalus, brain tumours, drug intoxication, alcohol intoxication, thyroid disease, parathyroid disease, and vitamin or other deficiencies also need to be excluded when appropriate.

The inclusion criteria, exclusion criteria, examinations, methods of examination and evaluation should be carefully described and documented in the study protocol.

### *4.1.5 Early and advanced stages of disease*

Based on the modest progress in the treatment of dementing conditions with moderate to severe impairment interest has grown to diagnose and treat subsyndromal or very early stages of these diseases as soon as possible. So recently, mild cognitive impairment (MCI) was proposed as a nosological entity in elderly patients with mild cognitive deficits but without the complete picture of dementia and as such has become an area of high research interest. The rationale behind the development of this term is that an individual patient will pass through a stage of impaired cognition without social or occupational impairment and that the start of treatment in this early stage will result in greater benefits. This new term shows overlapping with other definitions as "benign senescent forgetfulness", "age associated memory impairment", "age associated cognitive decline" and "cognitively impaired not demented". However, the concept of MCI suffered from several limitations. Estimations of prevalence from epidemiological studies are highly variable depending on the used definitions and criteria. A high proportion of patients diagnosed with MCI returned to normal without progression to dementia, on the other hand in several studies rates of progression from MCI to the full spectrum of dementia up to 12 percent per year have been described. Data from clinical trials using cholinesterase-inhibitors and other medicinal products with different mechanisms of action in patients with MCI have not shown efficacy in the predefined primary endpoints. Thus up to now MCI is not considered as a homogeneous clinical entity and more work on characterization of meaningful diagnostic criteria is needed, particularly the multiplicity of MCI definitions, the role of aetiological subtypes (e.g. amnestic type of MCI) and the development of appropriate assessment tools has to be refined. Currently epidemiological and clinical studies are underway to establish validated criteria for definition of "pre-dementia stages" (see 4.1.3).

In advanced stages of dementia the focus of the impairments for the patients and carers is changing. Beside the cognitive deficiencies functional impairments are more and more pronounced and stabilization or improvement in ADL may be more important endpoints. Behavioural problems with agitation and aggression do occur with major impact on patients and carers. Not many studies have been performed in patients with severe dementia, so there is a need for adaptation of assessment tools, which allow a comprehensive evaluation of the cognitive and the functional domains with special emphasis on ADL and behavioural abnormalities.

## 4.2 Assessment of Therapeutic Efficacy

### *4.2.1 Criteria of efficacy*

*Symptomatic improvement*

Improvement of symptoms should be assessed in the following three domains:

1) cognition, as measured by objective tests (cognitive endpoint);

2) activities of daily living (functional endpoint).

3) overall clinical response, as reflected by global assessment (global endpoint).

Efficacy variables should be specified for each of the three domains. Two primary endpoints should be stipulated reflecting the cognitive and the functional domain. The study and its duration should be designed to show significant differences in each of the two primary variables. Global assessment should be evaluated as a secondary endpoint.

If this is achieved, then an assessment should be made of the overall benefit (response) in individual patients, and the effect of treatment should be illustrated in terms of the proportion of patients who achieve a clinically meaningful benefit (response) defined based on consideration of the natural progression of disease for the specific setting, e.g. for a claim of short term treatment, responders (in patient populations with AD, PDD or DLB) may be defined at 6 months as improved to a relevant pre-specified degree in the cognitive endpoint and at least not worsened in the two other domains. Depending on the natural course of the dementia subtype longer duration of clinical trials are required, e.g. in VaD it has been shown that at least 12 months seem to be necessary. Other definitions of responders are possible, but should be justified by the applicant, taking into account the clinical relevance of the outcome.

Secondary endpoints of interest may include neuropsychiatric and behavioural symptoms. For a claim in these symptoms, the trial should be designed with neuropsychiatric and behavioural symptoms, measured according to a specific and validated scale, as part of the confirmatory testing strategy (see 4.2.2 *Choice of tools*). It may be preferable to address these additional hypotheses through a separate specific trial.

In the more advanced forms of the disease, changes in cognitive performance may be less relevant to quantify. Hence choice of functional and global domains as primary endpoints may be more appropriate to establish clinically relevant symptomatic improvement in this severely impaired population.

*Disease modifying effects*

Up to now no clinical trial has led to a successful claim of disease modification in dementing conditions. For regulatory purposes a disease modifying effect will be considered when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by an improvement of clinical signs and symptoms of the dementing condition. Consequently a true disease modifying effect cannot be established conclusively based on clinical outcome data alone, such a clinical effect must be accompanied by strong supportive evidence from a biomarker programme. As this is difficult to achieve without an adequately qualified and validated biomarker, a two-step approach may be more suitable. If in a first step delay in the natural course of progression of the disease based on clinical signs and symptoms of the dementing condition can be established, this may be acceptable for a limited claim, e.g. delay of disability. If these results are supported by a convincing package of biological and/or neuroimaging data, e.g. showing delay in the progression of brain atrophy, a full claim for disease modification could be considered.

*Primary prevention*

The overall goal of primary prevention in dementia is to reduce the incidence of the disease. This will be accomplished by promoting the initiation and maintenance of good health or by removing potential causes of disease in non-demented individuals or individuals with potentially modifiable (e.g. hypertension, high cholesterol) or unmodifiable (APOE4 status, high age) risk factors for dementia. Cognitive endpoints in primary prevention trials have been dementia (based on cut-off scores), significant cognitive decline and change in cognitive function based on longitudinal

performance on certain tests. Unfortunately trials so far have not given conclusive results, however, this may be due to methodological reasons, e.g. high baseline variability and heterogenous populations, ceiling effects of assessment tools, rarity of proposed outcome, etc. Therefore in future prevention trials baseline populations, length of follow-up, timing in relation to possible dementia onset, use of valid outcomes, which are sensitive to change, etc. must be considered and should be justified (see also Section 4.1.5).

### *4.2.2 Study design and methods*

*Run-in period*

The screening and run-in period, preceding randomisation to treatment is used for wash-out of previously administered medicinal products which are incompatible with the trial, and for the qualitative and quantitative baseline assessment of patients.

*Choice of control group*

In many countries symptomatic treatment of dementia with cholinesterase-inhibitors is considered as standard of care, particularly in mild to moderate Alzheimer's disease. Therefore in the future new treatments for dementia may be evaluated more and more by using add-on-designs, particularly in long term studies the "pure" use of placebo control for demonstration of efficacy may be difficult to justify. However, substantial differences between placebo patients in the different trials and distinct subtypes of dementia have been shown, therefore placebo controlled studies are still necessary.

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 for symptomatic improvement. However, due to concerns over assay sensitivity, the use of a non-inferiority design versus active control only will not be accepted as proof of efficacy. Therefore three-arm studies with placebo, test product and active control or a superiority trial are the preferred design options. As feasibility of long term placebo controlled studies 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 trial of shorter duration (e.g. 6 or 12 months depending on the dementia subtype) and thereafter to switch placebo patients to a predefined active treatment or randomise them to the experimental product or a predefined active treatment.

*Choice of tools*

Measurement tools (cognitive, functional or global) should be externally validated, pertinent in terms of realistically reflecting symptomatic severity, sufficiently sensitive to detect modest changes related to treatment, reliable (inter-rater; test/retest reliability) and as far as possible easy to use and of short duration, allowing the possibility of easy combination with other tests. They should be calibrated in relation to various populations with distinct dementia syndromes and subpopulations of different social, educational and cultural backgrounds in order to have validated norms available for the interpretation of the results. Particularly in early stages of the distinct dementia subgroups better tools for cognitive, functional or global assessments with higher sensitivity to change are needed and would be welcomed.

They should be standardised for use in different languages and cultures. Some tools (e.g. memory tests) should be available in several equivalent forms to allow for the effect of training with repeated administration.

Applicants may need to use several instruments to assess efficacy of putative drugs for treatment of dementing conditions because:

a) there is no single test that encompasses the broad range of heterogeneous manifestations of dementia and its specific subtypes

b) there is no ideal measurement instrument at the present time. Whilst a large number of methods for evaluation of cognitive functions and behavioural changes have been suggested, none has convincingly emerged as the reference technique, satisfying the above set of requirements. Hence the choice of assessment tools should remain open, provided that the rationale for their use is presented, and justified

c) demented patients are poor observers and reporters of their own symptoms and behaviour self-report measures tend therefore to be less sensitive to treatment effects than observer-related instruments, particularly in moderate to severe disease stages. Relatives or nurses evaluations should therefore be part of the assessment, even though the risk of bias should not be underestimated.

For each domain one instrument should be specified in the protocol as primary. It is recommended that each domain is assessed by a different rater who should be independent of and blind to all other ratings of outcome. If side effects exist which can unblind the investigator, all outcome raters should be denied access to this information as far as possible. In advance, and if necessary, the raters should be trained so that variability is minimised and inter-rater reliability is maximised with the assessment tools used.

The applicant will be required to justify the instruments selected with respect to their psychometric properties and the population studied.

- **Objective cognitive tests**

Objective tests of cognitive function must be included in the psychometric assessment; such tests or batteries of tests must cover more than just memory as impairments in domains other than memory are mandatory for the diagnosis of AD and the assessment of its severity. Within the domain of memory, several aspects should be assessed. These are learning of new material, remote as well as recent memory, and recall and recognition memory for various modalities (including verbal and visuo-spatial). Other cognitive domains such as language, constructional ability, attention/concentration, executive functions and psychomotor speed should be assessed as well.

The Alzheimer's Disease Assessment Scale (ADAS) cognitive subscale, dealing with memory, language, construction and praxis orientation, is widely used and can be considered as standard in trials on patients with mild to moderate Alzheimer's disease. However, due to ceiling and floor effects, its sensitivity to change is limited in early and late stages of the disease. . If new instruments are developed, data are needed to provide empirical support for the construct validity and reliability of the new measurement tools (e.g. test-retest, inter-rater, internal consistency, etc). Moreover, for correct interpretation of the described results validation of these tests in normal controls and different disease states including influences by age, gender, level of education, time interval of testing etc. is necessary. Otherwise the clinical meaningfulness is not assessable. For instance the ADAS-cog has been adapted to vascular dementia by adding assessment of executive function as Vascular dementia Assessment Scale (VaDAS), however, comprehensive data on validity and reliability have not been published yet.

Alternatives to the ADAS like the "Neuropsychological Test Battery for Use in Alzheimer's Disease" (NTB) or others have been validated and may be used. However, it has to be taken into consideration that every scale must be adapted and validated for the distinct subtypes of dementia, and within subtypes the original validated scale should be used without further adaptations. If other scales than $ADAS_{cog}$ are used as primary outcome measure, estimations with the $ADAS_{cog}$ as secondary endpoint should supplement the results for consistency of interpretation.

- **Self-care and activities of daily living**

Activities of daily living (ADL) assessment is useful to evaluate the impact of a medicinal product-related improvement in everyday functioning. These measurements usually rely largely upon the reports of relatives or carers in close and regular contact with the patient, some items of measurement are gender- and culture-biased.

Several scales have been proposed to measure either basic activities of daily living (or self -care) which relate to physical activities, such as toileting, mobility, dressing and bathing (ADL) or instrumental activities of daily living, such as shopping, cooking, doing laundry, handling finances, using transportation, driving and phoning (IADL). However, this concentration on common self-care or domestic activities disregards many activities, which in recent times may be more appropriate, e.g. use of technology. This results in low sensitivity to change of most of the used assessment scales today. Separate measurement tools of ADL/IADL for early and advanced disease stages are needed, which add new dimensions to the existing assessment tools to allow better evaluation of a clinically meaningful change, e.g. in epidemiological studies impairments in four IADL items (handling medications, transportation, finances and telephone use) have been shown as most sensitive indicators

of early stages of dementia (particularly when performance speed is taken into consideration) whereas in advanced disease stages basic ADL as toileting, dressing and bathing are sensitive indicators of change. One of the major issues for use in clinical trials is non-linearity of these changes over time due to adaptation and coping strategies of the individual patient. However, in newer studies using the "Disability Assessment in Dementia" (DAD) or the "Alzheimer Disease Cooperative Study ADL scale" (ADCS-ADL) some initial results showed linearity in change over one year in mild to moderate AD.

As many instruments are under further study in the study protocol choice of the instrument for assessment and its applicability for the distinct dementia entity and early or advanced disease stages should be justified.

- **Global Assessment of Change**

Global assessment refers to an overall subjective independent rating of the patient's condition by a clinician experienced in the management of patients with dementia. Despite certain limitations, the clinician's global assessment can serve as a useful measure of the clinical relevance of a medicinal product's anti-dementia effect. Moreover, global assessment, being in general more unspecified, allows detection whatever changes occur within treatment.

A global scale allows a single subjective integrative judgement by the clinician on the patient's symptoms and performance, as opposed to assessing various functions by means of a composite scale or a set of tests (comprehensive assessment). The Clinician's Interview Based Impression of Change-plus (CIBIC-plus) allows assessment of the global clinical status of the demented patient relative to baseline, based on information from a semi-structured interview with the patient and the carer, without consideration of any cognitive performance from any source. The Alzheimer's Disease Cooperative Study Unit Clinician's Global Impression of Change (ADCS-CGIC) is another semi-structured interview based global measure incorporating information from both patient and carer. Compared to the CIBIC-plus it is more specified with focus on 15 areas including cognition, behaviour and social and daily functioning. Although such a global assessment of patients benefit is less reliable than objective measurements of response and often appears insufficient to demonstrate by itself an improvement, it should be part of clinical trials in dementia as it represents a way to validate results obtained in comprehensive scales or objective tests, particularly when it is applied by an independent rater. The CIBIC-plus has been shown to be less responsive to drug effects than psychometric tests alone in some studies with anti-dementia drugs in AD, however, clinical global impression was more sensitive than standard measures of cognition and behaviour in a study in patients with PDD.

Contrary to global measurement of change, comprehensive assessment is meant to measure and rate together in an additive way several domains of the illness, e.g. cognitive deficits, language deficits, changes in affect and impulse control. Scores proven to be useful in describing the overall clinical condition should be used, such as the Clinical Dementia Rating (CDR).

However, rather than composite scores derived from summing or averaging scores in different domains, the use of a set of instruments to quantify individually the dimensions of impairment, disability and handicap (social participation) is encouraged by regulatory bodies.

- **Health related quality of life**

Although quality of life is an important dimension of the consequences of diseases, the lack of sufficient validation of its assessment in dementia does yet not allow specific recommendations to be made for regulatory acceptance. Further studies are required to validate adequate instruments for assessment of these dimensions in patients and their caregivers. In theory, both generic and disease specific questionnaires may be used in patients with dementia. However, in practice, it is very important to choose a questionnaire which addresses the key domains of the disease and is sensitive to reflect clinically meaningful changes. Depending on the disease stage information regarding quality of life can be obtained by the patient, by family members or professional caregivers. Based on the different perspectives of the respondent – patient or carer - the information may be divergent and sometimes even contradictory. This has to be taken into consideration in the process of validation of semi- or structured interviews and assessment scales before claims about improvement in quality of life can be achieved. The issue is further complicated by "response shift". This term reflects on the change in the internal standards of the respondent: based on psychological, social and cultural

background and resources coping processes will be facilitated, which may lead to an improvement in quality of life independent from treatment with medicinal products for dementia. These effects are clearly different in early and advanced stages of the dementing condition and must be taken into consideration.

Examples for disease specific quality of life measures are the Alzheimer's Disease-Related QOL (ADRQL) and the QOL-Alzheimer's Disease (QOL-AD), both show sufficient psychometric properties and studies are ongoing to establish their sensitivity to change. Similar instruments should be developed for other dementing conditions as well.

- Behavioural Signs and Symptoms

Although the formal clinical diagnostic criteria do not include behavioural signs and symptoms, they are an important cause of clinical deterioration in patients with dementia and are associated with increased burden of disease and stress particularly for family members or caregivers. The overall frequency and severity of behavioural abnormalities increase in the later and more severe stages of dementia. Among the most frequent and disturbing behavioural symptoms are apathy, agitation, aggression and delusions. However, individual behavioural symptoms have been described as highly variable and heterogeneous in presentation, transient, recurrent or persistent in course and fluctuating in prevalence and severity.

Several assessment tools like the Behavioural Pathology in Alzheimer's disease Rating Scale (BEHAVE-AD), the Behavioural Rating Scale for Dementia (BRSD), the Neuropsychiatric Inventory (NPI) and others have been used as outcome measures in clinical trials,

## 4.3 General Strategy

The following recommendations apply to all dementing conditions but have to be adapted to the specific forms of dementia (e.g. Alzheimer's disease, vascular dementia, etc.).

**Exploratory Studies**

### *4.3.1 Early pharmacology and pharmacokinetic studies*

In the early phases of the development of anti-dementia medicinal products it is important to establish the pharmacological rationale on which the drug may be thought to be effective. Side effects and possible surrogate markers of pharmacological activity in volunteers, if available and relevant, might give some estimation of the appropriate dose.

Standard pharmacokinetic studies (see Note for Guidance on Pharmacokinetic Studies) must aim at defining the absorption, distribution, metabolism and elimination of the drug.

Pharmacokinetic interactions between the test drug, other anti-dementia drugs and other medicinal products, expected to be given concurrently in clinical practice, should be studied, unless clear mechanistic based evidence is available that no interaction could be expected.

Pharmacodynamic interactions between the test drug and any psychoactive medicinal product, expected to be given concurrently with the test drug in clinical practice, should be studied.

If relevant, pharmacokinetic studies of the test-drug in patients with hepatic and /or renal impairment should be performed.

### *4.3.2 Initial therapeutic trials*

As it is difficult to seek improvement and probably unrealistic to expect recovery in advanced dementia, efficacy studies are expected to be carried out mainly in patients suffering from mild or moderate forms of the disease. The inclusion of the same type of patients in Phases II and III is advised, as safety issues may not be the same in different subgroups. Ideally such studies are carried out in the patient's everyday surroundings. These studies in well-characterised samples of demented patients have the following objectives:

- preliminary evaluation of efficacy
- assessment of short-term adverse reactions from a clinical and laboratory standpoint
- determination of pharmacokinetic characteristics

- definition of doses presumed to be effective
- determination of maximal tolerated doses

The duration of such trials will depend either upon the time of response that is expected, or may be one of the parameters to be assessed. Newer techniques as MRI (e.g. atrophy of entorhinal or parahippocampal cortex) or others may be used as biomarkers in such Phase II-trials. As the use of such biomarkers has been improved considerably they may be used as primary endpoint in proof of concept studies or as secondary endpoints in pivotal clinical trials.

**Confirmatory Studies**

### *4.3.3 Controlled clinical trials*

*Symptomatic improvement*

Symptomatic improvement studies have the following main objectives:

- demonstrating efficacy of the drug and estimating the temporal course and duration of such effects
- assessing medium and long-term adverse effects.

Controlled clinical trials aimed at demonstrating short term improvement in AD should last at least 6 months. In epidemiological studies and clinical trials in patients with VaD it has been shown that cognitive and functional decline is slower than in AD, here study durations of at least 12 months seem to be necessary to show a difference between active and placebo treatment. These studies should include placebo and/or comparators where appropriate. However, even longer study durations are required to establish the maintenance of efficacy, e.g. by randomized withdrawal designs. The results of such extended studies might have an impact on labelling of compounds demonstrating efficacy. Depending on the subtype of dementia the possible influence of co-medication has to be taken into consideration, e.g. changes of dopaminergic treatment in PDD or changes of cardiovascular medication in patients with VaD.

Follow-up of at least 6 to 12 months more than in short term studies is recommended for demonstrating long term safety. This can be achieved with an extension of the trial over the initially scheduled period in patients considered as responders and/or asking for continuing the treatment. In addition to responding adequately to an ethical issue, this allows to accumulate data on medium/long term safety of the drug and to estimate the maximal duration of the symptomatic effects.

Periodic evaluation of efficacy and safety should be performed at regular intervals, depending on the anticipated rapidity of action of the medicinal product and the duration of the trial. After the end of the treatment administration, the state of the patients should be followed for possible adverse events related to withdrawal treatment for a period appropriate for the drug being tested.

*Disease modifying effects*

From a regulatory point of view, a medicinal product can be considered as disease modifying, if the progression of the disease as measured by cognitive and functional assessment tools is reduced or slowed down and if these results are linked to an effect on the underlying disease process (see also Section 4.2.1 *Disease modifying effects*).

In order to establish an impact on disease progression, distinction between symptomatic and disease modifying effects of a medicinal product has to be made: unfortunately there is no ideal study design to show unambiguously a disease modifying effect. Due to the characteristics of the underlying disease and if only slowing of the disease process is foreseen as a possible outcome, long-term placebo controlled trials are needed, and clinical outcomes in both study arms are measured at regular intervals to establish a clinically relevant effect. Clinical improvement must be shown over a time period that is relevant to the proposed claim taking into consideration the distinct subtype of dementia and its natural course. The minimum duration of confirmatory trials depends on the expected progression rate and the assumed activity of the experimental compound, e.g. in patients with mild to moderate Alzheimer’s disease, duration of 18 months has been assumed to be sufficient in some currently ongoing trials. So in a first approximation a hypothesis of disease modification seems most consistent with a statistical comparison of rates of change in clinical symptoms over time (slope analysis).

However, it should be taken into consideration that although it is known that the natural course of disease may be approximated with a linear model over time, it is yet unclear, whether a linearity assumption holds true in the situation of a clinical trial with an intervening (potentially disease modifying) treatment effect and whether the effect of treatment is constant over the treatment course. The specification of the statistical model for the slope analysis is, therefore, not straightforward. Moreover, treatment effects are often different over the various disease stages (mild, moderate, severe) and many of the most commonly used outcome measures show a non-linear change, when used for time periods longer than one year.

In consequence it should be established that at (at least) two distinct time points the treatment effect in the pre-specified endpoints demonstrably increases over time in a parallel group design. Such a study can be enhanced at the end of the trial with a phase of a randomized delayed-start or randomized withdrawal design. The magnitude of the treatment effect in terms of established outcomes, e.g. $ADAS_{cog}$ and ADL, is estimated based on the difference between placebo and experimental compound at study end. If there are key clinical milestones of the disease that are driven by the underlying disease process, and not just the symptoms, then the possible disease modifying effect may be addressed by a survival analysis comparing time to 'milestone' event. Alternatively, the possible disease modifying effect may be addressed by a simple slope analysis supported by a time to event approach. Either analysis must be supported with additional evidence on the underlying disease process.

Both approaches to establish a disease modifying effect have their drawbacks and may be further hampered by possible placebo response, differences in drop out rates and missing data in general, poor adherence to treatment, change of treatment response with course of disease, etc. Therefore the choice of primary analysis, specification of the statistical model and the fulfilment of underlying assumptions and requirements should be justified in detail in the study protocol.

Independently from the study design chosen it may be difficult to differentiate unambiguously between symptomatic and disease modifying effects only on the clinical endpoints, therefore a full claim of "disease modification" can be supported by evidence from suitable study design, accepted novel analyses, or an adequately qualified and validated biomarker, which is able to indicate an effect on the underlying pathophysiology of the dementia syndrome. Such a biomarker should reflect key aspects of the underlying disease process based on a plausible disease model (see also Section 4.2.1 *Disease modifying effects*).

### *4.3.4 Adjustment for prognostic variables*

Based on theoretical, experimental or observational considerations, the course of the disease and/or the efficacy of treatments may differ within subgroups of patients with dementia or its specific subtypes.

Some examples of prognostic factors to take into consideration could be as follows:

- apolipoprotein E genotype
- profile of betaamyloid and tau-protein in cerebrospinal fluid
- neuroimaging parameters (MRI, serial MRI, emission tomography)
- suspicion of Lewy body pathology (fluctuation of cognition, hallucinations, Parkinsonism)
- severity of dementia at inclusion
- presence of vascular risk factors.

The factor(s) to be taken into account in the analysis should be identified in the protocol, the rationale should be given, and the study should be powered to yield a sufficient number of patients with or without the factor(s) such that consistency of effects across important sub-populations (internal consistency) can be demonstrated. Moreover, some of these variables may be used to predefine homogeneous patient populations at risk ('enriched populations'), which may allow better exploration of therapeutic efficacy in distinct populations.

### *4.3.5 Concomitant treatments*

In order to eliminate any interference or bias, it is desirable, particularly in exploratory trials to avoid any treatment likely to impair alertness, intellectual function and behaviour. These include hypnotic,

anxiolytic, antidepressant, antipsychotic, anticholinergic and memory enhancing drugs. If they cannot be avoided, the acceptable level of use of such medicinal products should be set a priori in the protocol and remain constant throughout the trial.

Pharmacodynamic interaction studies between the test drug and the drugs commonly used in the elderly should be conducted, including psychotropic drugs used to control behavioural disturbances as mentioned earlier.

## 4.4 Safety Evaluation

In general the content of ICH E1 should be taken into consideration.

Identified adverse events should be characterised in relation to the duration of treatment, the applied dosage, the recovery time, particularly the different age groups (e.g. old and oldest-old patients) and other relevant variables. Clinical observations should be supplemented by appropriate laboratory tests and electrophysiological recordings (e.g. electrocardiogram). It should be considered that the acceptance of adverse events in patients with early disease stages and minor impairment will be different in benefit-risk assessment than in patients with advanced disease stages and severe impairment.

All adverse events occurring during the course of clinical trials must be fully documented with separate analysis of serious adverse drug events, adverse events leading to drop-outs and patients with a fatal outcome.

Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self poisoning should be provided, particularly in the patients with mild to moderate cognitive impairment.

Special efforts should be made to assess potential adverse effects that are characteristic of the class of drugs being investigated depending on the action on distinct receptor sites, e.g. cholinomimetic effects of cholinesterase inhibitors.

### *4.4.1 Neurological adverse events*

Depending on the dementia subtype special attention should be given to the occurrence or exacerbations of neurological adverse events, particularly cerebrovascular events, extrapyramidal symptoms, disorientation, further impairment of gait, occurrence of seizures, etc.

Also the effect of withdrawal of the test drug should be systematically monitored.

### *4.4.2 Psychiatric adverse events*

Depending on the dementia subtype specific attention should be paid to the occurrence of hallucinations and other signs and symptoms of affective or psychotic disorders. Other neuro-behavioural abnormalities, particularly disorientation, agitation and aggressive behaviour should be recorded depending on the pharmacodynamic profile of the test drug. Specific claims in this respect, e.g. improvement of neuro-behavioural abnormalities, have to be based on specific studies (see 4.2.1 *Symptomatic improvement* and 4.2.2 *Choice of tools*).

### *4.4.3 Cardiovascular events*

Depending on the dementia subtype and the pharmacodynamic profile of the medicinal product its effects on the cardiovascular system, e.g. occurrence of orthostatic hypotension, the potential to induce arrhythmias, or increased risk of myocardial infarction should be monitored.

### *4.4.4 Long-term safety*

The total clinical experience must generally include data on a large and representative group of patients (see EC Guideline on population exposure), it should be considered that long term safety may be different in the distinct subtypes of dementia, e.g. AD vs. VAD and PDD and the different age groups.

For the moment, studies on morbidity and mortality are not required before marketing authorisation. However, effects on mortality should be monitored on a long term basis. This can be done post-marketing by implementing a risk minimization or risk management plan.

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## *10.3 Guidelines for the Clinical Evaluation of Antidementia Drugs*

# Guidelines for the Clinical Evaluation of Antidementia Drugs

First Draft

November 8, 1990

Paul Leber, MD

## 1. Purpose of the Guidelines:

This Guideline is one of a series of documents published by the FDA to assist sponsors in their development of new drug products. This particular guideline, dealing exclusively with antidementia drugs, provides detailed information about the nature of and basis for agency policies that may affect the scope and pace of premarketing product development.

These guidelines are intended primarily to provide advice about matters and issues relating to the planning, design, conduct and the interpretation of clinical investigations, investigations that must serve as the primary sources of evidence supporting claims for the safety and efficacy of new drug products.

The advice offered reflects what experts working in the field believe are scientifically sound approaches to a number of issues that in the past have posed difficulties for the developer of antidementia drugs. Hopefully, the sponsor who heeds the advice and suggestions offered will find the demanding task of commercial drug development much facilitated.

### *1.1. Definition of Dementia:*

sanguine assumptions and appeals to biologic plausibility, the drug has of unknown etiology that ordinarily causes a progressive, irreversible decline in intellectual and cognitive abilities. Although the syndrome of dementia presumably has many causes, this Guideline is intended primarily to provide advice about developing treatments for patients who would be deemed to suffer from Alzheimer's Dementia1

However, many of the principles enumerated in the guideline apply equally well to other types of chronic dementing illness. (e.g., multi-infarct dementia).

### *1.2. The nature of acceptable antidementia drug claims:*

The intended therapeutic use and/or claim made for an antidementia drug affects the nature of its development and testing. Clearly, a drug intended to prevent and/or reverse the dementing process will be evaluated under very different testing conditions than one intended to suppress psychotic behavior in an institutionalized, end stage patient.

These guidelines focus primarily upon treatments intended to affect the "core" phenomena of Alzheimer's Dementia. Although there are some minor disagreements about the identity of the core phenomena and their relative importance, experts generally agree2 that a treatment cannot be considered to exert an 'antidementia' action unless it beneficially affects a demented patient's ability to learn new and retrieve old, previously learned, information.

This does not, of course, preclude the development of drugs that affect other aspects of the dementing process (i.e., failed self care, disturbed mood, loss of control over impulses, etc.), but it does restrict the nature of the drug effects that will be granted an unmodified antidementia indication. Of particular importance, claims for actions artificially tied to dementia (i.e., so called 'pseudospecific' claims will not be allowed.3

A distinction is often made between symptomatic and definitive treatments; either are acceptable claims for an antidementia drug. Unfortunately, until the etiology and/or pathogenesis of the dementing process is fully understood, it seems unlikely that a definitive treatment for Alzheimer's will be developed.

More probably, antidementia drugs, at least in the near future, will be those that cause an improvement in,or slow the rate of deterioration of, the various functions (memory, reason, etc.) that fail increasingly as the dementing process progresses.

### *1.3. FDA's Regulation of Clinical Drug Testing: an overview:*

The Federal Food, Drug and Cosmetic Act, our domestic drug regulatory law, instructs the FDA to 'Promulgate' regulations governing the conditions under which clinical investigations of new drugs may be conducted4 . The Act makes plain that Congress, in issuing this instruction, sought the implementation of a system of drug regulation that would protect subjects participating in clinical investigations from unreasonable and/or unnecessary risks to their health and safety.

In view of this mandate, FDA's regulations and policies governing the clinical testing of newdrugs must "assure the safety and rights of subjects." However, because the development of effective treatments for serious illnesses such as Alzheimer's Dementia is very much in the interests of the public health, FDA's regulations and policies are also designed to enhance the "quality" of clinical investigations that are intended by sponsors to serve as sources of evidence supporting their New Drug Applications.

Thus, proposals to conduct clinical investigations are evaluated not only in light of the risks they impose upon human subjects, but for their capacity (i.e. by virtue of their design and protocol requirements) to provide a valid assessment of the therapeutic (or diagnostic) potential of the experimental drug under test. Accordingly, the regulatory assessment of proposed research protocols takes into account the nature of the illness for which the treatment is being developed, the availability of alternative treatments, all information relevant to the therapeutic potential and toxicity of the new drug, the type of clinical trial design proposed, and the adequacy of the plans for the actual conduct of the experiment (e.g., statistical power, nature of patient entry criteria, validity and reliability of assessment measures, etc.). In sum, the goal of regulation is to ensure that clinical research is conducted using valid designs under conditions that minimize the risk to subjects.

## 2. FDA's Regulation of Clinical Drug Testing: an overview:

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## *2.1. The Strategy and Tactics of Drug Development:*

### 2.1.1. Essential prerequisites of clinical drug testing

Prior to its use in humans, an investigational drug substance is evaluated in a battery of preclinical tests (i.e., in vitro, ex vivo, and in vivo tests) intended to identify its potential to cause structural injury and/or interfere with normal physiologic functions. Ordinarily, in vivo preclinical tests are conducted under conditions more extreme (i.e., in terms of duration and amount of drug) than those to which human subjects will be exposed. Clinical testing with a new drug is only initiated if the evidence adduced in an appropriate preclinical test battery provides reasonable assurance that the use of the drug will not cause immediate, irreparable harm or injury. 5

### 2.1.2. Early clinical testing

The pace of expansion of clinical testing (i.e., in terms of the total current and cumulative numbers of individuals exposed to an investigational drug) and the conditions under which clinical testing is permitted ( i.e., in terms of dose, cumulative dose, duration of exposure, setting for the experiment, quality and intensity of medical monitoring of subjects, etc.) is governed by the nature of information developed in clinical and preclinical experiments.

Clinical testing ordinarily begins with the exposure, under closely monitored medical supervision, of a few healthy individuals to single, comparatively low, doses of a drug6. If no serious untoward events or physiologic disturbances occur under these initial conditions, additional subjects are exposed to higher and/or repeated doses; in this manner, the common untoward and toxic effects associated with the use of the drug are identified. If dose (i.e., or equivalently, drug plasma concentration) dependent toxicities do not preclude it, volunteers are often exposed to doses of the drug that exceed those estimated (e.g., from preclinical data, or non-domestic clinical reports) to be necessary to achieve the desired therapeutic response in patients7. In this manner, a clinical pharmacological/physiologic/toxicologic profile of a new drug is compiled. As noted, the plasma (or effect compartment) drug concentrations at which these various drug associated phenomena occur is, ideally, also recorded, and this information, taken together with the results of additional, concomitantly conducted, preclinical studies, then serves as an ever widening informational base for decisions regarding the subsequent development and testing of the drug.8

### 2.1.3. The early demonstration of efficacy:

The testing of an experimental drug of undocumented value cannot be extended indefinitely. Because exposure to virtually any pharmacologically active drug imposes some potential risk, the exposure of large numbers of subjects to a drug that may be therapeutically ineffective or to an effective drug administered at subtherapeutic doses cannot be medically or ethically justified. Consequently, regulatory policy requires sponsors to document the efficacy of an investigational drug and characterize the conditions under which it expresses its therapeutic effect as early in the course of its development as possible.

In regard to the development of drugs for the treatment of dementia, this policy has important implications. Before the efficacy of an antidementia drug is documented (i.e., during phase 1 and early phase 2), open studies are justified only to the extent necessary to establish its maximum safely tolerated dose in volunteers and typical patients. Once this upper dose (or plasma concentration) range is delimited, there is no justification for additional uncontrolled use of the investigational drug because the spontaneous variability in the course of the dementia (in any given patient) makes uncontrolled investigations of efficacy pointless. Of course, after the efficacy of a drug is documented, open studies may be a preferred way to gain insights into the toxicities associated with its use (i.e., in Phase 3). This policy derives from the view that the exposure of large numbers of individuals to drugs of unestablished therapeutic value is an ethically arguable undertaking.

For the reasons just given, once a reasonable estimate for the range of doses and/or drug plasma concentrations presumed necessary to achieve a therapeutic effect has been obtained9 prospectively randomized controlled trials capable of definitively documenting the efficacy of the putative antidementia agent must begin. Again, because of the marked variation among patients with dementia (i.e., in terms of course, rate of deterioration in function, etc.), it is essential that these controlled trials compare one or more fixed doses (or narrow plasma concentrations) of the experimental drug with a placebo control10.

In the absence of an established treatment for dementia, a standard drug cannot be used as a control, per se; however, there is no objection to comparing a putative antidementia drug with another investigational agent thought to possess anti-dementia activity so long as the comparison includes randomized and blinded assignment of patients to a placebo control as well.

In sum, the process of drug development envisioned in regulations is dynamic and open-ended, the program for the clinical testing of a new drug undergoing continual iterative adjustment as new insights into its pharmacology, pharmacokinetics, risks, and therapeutic benefits are gained.

### *2.2. The Ultimate Goal of Drug Development*

By law, only safe and effective drug products can be marketed, but developing a product that can be judged 'safe for use' and 'effective in use' involves more than presenting results from clinical studies that document the product's superiority to some control treatment and that show that it can be administered with relative safety to a substantial number of patients.

Information and data must also be developed that will permit the sponsor to draft reliable instructions for the use of the product in the individual patient. Because response to a drug is a function of pharmacokinetic and pharmacodynamic factors that vary among patients, a single dosing regimen will not ordinarily be suitable for every patient.

To the extent that it is possible, therefore, sponsors should evaluate how age, race, sex, weight, concomitant medications and state of overall health affect response to treatment. This evaluation can be facilitated by assessing the extent to which these patient attributes affect population based estimates of the product's pharmacokinetic parameters (e.g., volume distribution, plasma clearance, etc.).

In sum, the ultimate goal of the government's regulation of drug product development is themarketing of safe and effective drug products with labeling that provides information that will allow the practioner to individualize the regimen for the drug's administration for those physiologic and demographic attributes that are known to affect treatment response.

## 3. Phases of drug development

### *3.1. Phase 1*

The goals of Phase 1 of drug development are, for most practical purposes, independent of the intended use of a drug. Consequently, the reader is also referred to the agency's General Guidelines for Drug Development which provide a more detailed discussion of thisfirst phase of clinical testing.

Phase 1 is the period during which the common untoward effects of a drug in humans are identified and initial estimates of its maximum tolerated dose (or plasma

concentrations) are developed. Phase I clinical pharmacology studies also provide an opportunity to characterize the disposition of a drug (i.e., obtain data on its absorption, distribution, metabolism and elimination (its ADME). Data obtained during single, rising dose and repeated multiple dose human safety/tolerance--studies can be used to estimate the fundamental parameters that depict the pharmacokinetics of a drug.

These estimates along with observations linking common untoward clinical effects and plasma concentrations of the drug and its metabolites are invaluable to those planning subsequent clinical trials. The value of acquiring this information early cannot be over emphasized; it is especially important in circumstances where the drug being developed has an intrinsically narrow therapeutic ratio. In such circumstances, knowledge of a drug's pharmacokinetic properties and maximum tolerated plasma levels may permit the sponsor to devise dosage formulations or dosing regimens that will substantially reduce the overall incidence of dose or concentration dependent untoward effects, effects that might ordinarily preclude the further development of the product.

Phase I is also the best time to discover whether or not a drug exhibits atypical pharmacokinetic properties (i.e., nonlinear kinetics, concentration or time dependent clearance, etc.). Again, acquiring this information early in development may allow sponsors to make timely decisions about the drug's potential as a commercial drug product.

In any event, by the end of phase 1, a sponsor should have exposed sufficient numbers of subjects to single and multiple doses of the drug to have identified the more common acute toxicities and physiologic actions of the drug up to doses (or plasma levels) exceeding those likely to be used (or be obtained) during phase 2 controlled trials.

To the extent permitted, the relationship between dose and/or plasma concentration and the outcomes observed should be assessed to determine if either dose, or plasma concentration predict the phenomena observed. At a minimum, enough basic information about the ADME of the drug substance and its metabolites should be available to allow intelligent planning of formal pharmacokinetic studies of the drug

in the formulations it will be used during phases 2 and 3. Before beginning phase 2, the sponsor should have sufficient information available to make an informed estimate of the doses and dosing regimens that should be explored during phase 2 controlled experiments.

### *3.2. Phase 2:*

Fundamentally, the goal of phase 2 is to document efficacy and identify the parameters of the treatment regimen (dose, dose interval, induction method, etc.) that are likely to maximize a product's therapeutic ratio in well characterized samples of demented patients. Because of concerns about needlessly exposing patients to ineffective, but pharmacologically active and, therefore, potentially harmful substances, phase 2 studies should patients to test the experimental null hypothesis). This is ordinarily accomplished by controlling sources of variance that tend to obscure modest treatment effects.

Accordingly, phase 2 studies commonly enroll samples of patients that have fewer medical illnesses and are less severely impaired than typical patients with dementia. To further enhance sensitivity, the sample selection process may employ maneuvers to increase the prevalence of patients thought likely to respond to the treatment. For example, in several recent (circa 1990) antidementia drug trials, patients were selected for study because they exhibited, during a pre-randomization phase, an apparently positive response to the investigational drug. While this sort of selection manoeuvre clearly undermines an experiment's external validity, it is a perfectly acceptable strategy in phase 2 where the goal is to demonstrate that the investigational drug has a therapeutic effect in at least some patients.11 In any event, there is ample opportunity to explore dose or plasma response relationships and the moderating effects, if any, of disease severity, stage, and various patient characteristics on the therapeutic response in subsequent clinical trials conducted after "preliminary evidence of efficacy has been gained i.e., in late phase 2, phase 3).

### *3.3. Phase 3:*

Phase 3 is traditionally the period during which a drug of established efficacy undergoes testing under conditions more representative of those which are thought

likely to prevail once it is marketed. As initially conceived, Phase 3 was intended to provide an opportunity to gain experience with the drug in settings more complex than those in Phase 2 investigations, which, as noted above, are often designed primarily to document a drug's efficacy under 'idealized' conditions.

In theory, testing a drug in relatively unstructured clinical settings will enhance the likelihood that risks specifically linked to its use in unique or vulnerable subgroups (e.g., the elderly, the severely ill, those receiving concomitant medications, those with renal or hepatic failure) will be identified prior to marketing. Unfortunately, even fairly large phase 3 studies involving one to two thousand patients are still too small to detect events that may prove to be common in certain subgroups within the population. One reason is that patients belonging to the vulnerable subgroup may simply not be represented in the typical drug development cohort.

In more recent times, in an effort to accelerate the pace of drug development, there is an increasing tendency to merge Phases 2 and 3 of drug development. In particular, it has become common to carry out large multiclinic investigations enrolling hundreds of patients to gather definitive evidence of both safety and efficacy. Indeed, the continued administration of an experimental drug (i.e., so called open extension protocols) to those who were participants in controlled investigations has become an important source of evidence used to document the safety of new drug products.

Unfortunately, this may produce a somewhat biased sample for evaluation, leading to the study of patients who are selected by virtue of their tolerance or preference for the drug. Thus, there is still a need, during Phase 3, to conduct large scale tests with patients who are naive to the product.

## 4. Design Issues

### 4.1.1. The need for internal controls:

The demonstration of antidementia efficacy requires a showing of a favorable difference between the investigational agent and an internal (concurrently randomized) control in a validly conducted clinical investigation.

The extent of variation among samples of patients drawn from the population with dementia is far too great to permit the use of non-concurrent (i.e. external) controls. Consequently, each clinical study intended to document the efficacy of an antidementia drug must include an appropriate 'internal , control as a means to determine whether the study's outcome, if nominally positive, can be unambiguously attributed to the effects of treatment with the experimental drug rather than to spontaneous fluctuations in the severity of the manifestations of the dementing process in the particular sample of patients evaluated13.

For studies evaluating antidementia treatments, placebo is the preferred choice for an internal control14; however, a subtherapeutic dose of the investigational drug or some less than optimal therapeutic dose of some other pharmacologically active agent might, provided certain conditions15 are met, be used instead. Regardless of the type of control employed, evidence of efficacy derives from a showing that patients randomized to the investigational drug fare significantly better than those concurrently randomized to the control.

### 4.1.2. The value of the fixed treatment level design.

Beyond demonstrating that a product is 'effective,' phase 2 studies should attempt to assess the link between dose (or drug plasma concentration), and dosing regimen (drug plasma level fluctuations) and both therapeutic and untoward responses. Ordinarily, this is best accomplished using study designs that randomize patients to two or more fixed 'levels' of experimental treatment16. Critically, 'fixed treatment level' designs do not require that patients be randomized to their final, full predetermined dose on the very first dose or day of treatment. Indeed, such a rigid dosing policy can, if a drug has many dose or plasma concentration dependent side effects, cause a fixed treatment level design to fail (patients assigned to the higher dose levels selectively dropout for adverse reactions). In such circumstances if there is any chance that tolerance to dose related side effects will develop, patients assigned to higher treatment levels should be gradually titrated to their predetermined dose or plasma concentration. This strategy is acceptable so long as 1) the levels of treatment (dose or concentration) assigned are specified prior to the experiment, 2) the outcome assessment for each treat ent level is made after steady state is achieved and sufficient time has elapsed to allow the full therapeutic response to develop under these

stabilized conditions, and 3) a parallel gradual dosing strategy is employed for those assigned to lower doses or concentrations to avoid inadvertent disclosure of treatment assignment to those responsible for the management of patients to preclude.

Incidentally, in the absence of a standard treatment for dementia, there is no meaningful 'active' control that can be used in studies of experimental antidementia agents.

Importantly, however, even if a drug were approved for use in the treatment of dementia, it would not remove the need for documenting the efficacy of a new antidementia drugs, in clinical trials with established 'assay sensitivity.'17

Given the foregoing discussion, it is clear that one preferred approach to the assessment of a new antidementia drug would involve the use of a clinical trial design that calls for the randomization of subjects to treatment with placebo and 3 widely separated, fixed18, dose levels (or plasma concentration ranges) of the drug. This parallel, fixed treatment-level design is not only capable of documenting a drug's efficacy, but it can also provide preliminary information about the relative toxicity and benefits of the various dosing regimens employed in the experiment.

#### 4.1.3. Parallel and cross-over designs:

Ordinarily, parallel designs are considered superior to crossover designs for the study of antidementia treatments. In theory, however, a crossover design may be employed if its treatment periods are relatively short and carry-over effects and/or withdrawal effects associated with the use of the drug are so insignificant that they are unlikely to confound the experiment's interpretation. Unfortunately, the existence of carry-over and withdrawal effects are commonly discovered only after the completion of a study at the time its results are being analyzed. In any case, if a sponsor does conduct a study using a cross-over design, it must be carried out in a manner that will permit its assumptions (i.e., no carry-over, no withdrawal, no treatment by period interactions) to be reliably evaluated from evidence developed in the experiment (i.e., there must be enrollment of sufficient numbers of subjects to provide adequate power to test for the presence of these confounding effects). In particular, the sponsor must document that patients entering any period of the design other than the first have returned to the clinical state they exhibited prior to the start of that first period. If this cannot be

demonstrated, the sponsor will have to explain why the assumptions of the design have not been violated.

Additionally, the sponsor electing to use a cross-over design in any study lasting more than a week or so, must be prepared to defend the suitability of the design for the evaluation of an antidementia drug, especially one that is intended for chronic administration.

Given the issues discussed, the presumed advantage of the crossover design (i.e., a reduction in variance contributed by between subject differences) may not be sufficient to overcome its liabilities.

### *4.2. The choice of experimental conditions:*

#### 4.2.1. The inter-relationship between the testing environment and the nature of the patients studied.

A controlled trial of a new drug can be carried out in virtually any setting given appropriate planning and resources. Often, however, especially early in Phase 2, concerns about the potential risks of the drug preclude testing in ambulatory patients living outside a medically supervised environment. The problem ordinarily is not that a drug is known affirmatively to be dangerous, but that the limited experience gained during phase 1 clinical testing cannot provide sufficient reassurance about the drug's safety 'for use,' at least under minimally supervised or unsupervised conditions.

Sponsors are understandably reluctant19, however, to ask ambulatory demented patients to enter medically supervised environments for the sole purpose of participating in a study. The hardship imposed upon such patients may be somewhat reduced if testing is split between inpatient and ambulatory environments. For example, induction and dose titration can be accomplished within a medically supervised environment. After a period of time judged sufficient to establish steady state plasma concentrations at the maximum dose to be given, patients may be discharged to their usual place of domicile provided that monitoring of treatment continues at frequent intervals.

Ideally, monitoring would include frequent sampling of blood levels of the drug to mitigate any risks associated with accumulation of the drug.20 An alternative strategy is to initiate controlled phase 2 testing of a new anti-dementia drug in more severely impaired-patients who are already institutionalized. Some may fault this approach, arguing that it is more difficult to document drug effects, at least on the core phenomena of dementia, in such advanced patients. On the other hand, even if such studies fail to provide definitive evidence of an antidementia effect, they may provide valuable insights about the nature of the drug's therapeutic action (i.e., positive trends) and insights into the nature of the drug's dose related toxicities. This information may then serve as a basis for the initiation of trials that can be conducted in ambulatory settings with less impaired patients.

In any case, once there is sufficient information to justify the use of the drug in outpatients, studies to evaluate the effects of antidementia drugs can be initiated in patients who are 1) free of concomitant illnesses, 2) taking no or few other active pharmacologic agents, and, critically, 3) still well enough to cooperate fully in the evaluation process which may be quite exhausting for even relatively unimpaired elderly normals.

Clearly, mildly ill patients of the sort just described are not representative of the population of elderly demented patients. However, it is widely believed that mildly ill patients will be more likely to respond to treatment than those with advanced disease21. As the primary goal of phase 2 is to establish efficacy, the potential gain in efficiency from us-ing mildly ill patients seems worthwhile even in the face of some loss in the trials external validity.

### 4.2.2. Subject selection criteria:

#### 4.2.2.(a). Diagnosis

Ordinarily, subjects enrolled in a study intended to document the efficacy of an antidementia drug should meet standard, widely accepted, diagnostic criteria (e.g., DSM-IIIR or those of the NINDS/ADRDA)22. However, mere specification of the diagnosis required for entry is not sufficient. Protocols for studies that are intended to serve as sources of 'substantial evidence of efficacy' must specify the actual tests,

criteria, and maneuvers required to meet the inclusion and exclusion diagnostic criteria being employed. For example, it is not sufficient to say that thyroid disease will be excluded by appropriate tests; rather, a specific test or tests, cut score criteria, and test methodology must be specified in the protocol. Moreover, the final study report must provide documentation to show that the findings of the tests required by the protocol did not require the subject's exclusion for thyroid disease.

The point is that there must be adequate documentation for assertions made about the characteristics of patients participating in clinical studies that are to presented in NDAS. This applies to reports and findings regarding physical examinations, laboratory tests, performance tests, behavioral ratings, etc.

Special efforts should be taken to document that the patients selected do not suffer from a condition that may be confused clinically with dementia. In particular, it is important to document that patients do not suffer from retarded depression (i.e. pseudodementia), delirium, or some primary neurologic or systemic illness that can mimic dementia (e.g. normal pressure hydrocephalus, Parkinson's disease, brain tumor, myxedema, drug-induced deliriform illness, etc.).

### 4.2.2.(b). Subject classification by stage and severity of illness

The stage and severity of the dementia affecting each subject participating in a clinical trial must be assessed and recorded systematically in a manner that will be readily understood by other workers in the field. In the absence of such information, it is virtually impossible to reach'any sort of valid conclusion about a clinical trialls external validity. Knowledge about stage and severity may also affect the chances of replicating successfully the results of a positive study.

Unfortunately, a standard system for describing the severity and stage of dementia has not yet been adopted by those working in the field. Nonetheless, this difficulty notwithstanding, reports of clinical trials acceptable for regulatory purposes must provide 1) an estimate of each patient's stage of dementia on some instrument with clinically understandable anchor points that has gained a reasonable degree of acceptance within the community of experts (e.g., Reisberg's Global Deterioration Scale) and 2) a measure of each subject's performance on some objective comprehensive test of cognitive function. Examples of the latter include the Mini-

Mental Status Exam (MSSE) (Folstein et al. 1975), the Alzheimer's Disease Assessment Scale (ADAS)(Rosen et al., 1984], the Memory Information Test (MIT) (Blessed et al., 1968), and the Dementia Rating Scale (DRS) of Mattis (Coblentz et al., 1973).

Although not a regulatory requirement, the use of the same assessment battery for staging and severity assessment in all major clinical trials of a sponsor's drug development program is encouraged.

As to specific choices, the agency cannot endorse the use of particular instruments. A sponsor would be well advised, however, to choose tests and instruments that have face validity and are viewed as acceptable by a large number of experts working in the field. It is unlikely that any one test or approach will gain the endorsement of all authorities, but it is better to employ a test that has been used widely (i.e. by different investigators) than one which is the 'pet' project of a particular individual or institution.23

The recommendations offered are in no way intended to discourage the use of non-clinical methodologies for the classification of patients. To the contrary, there is a need to develop independent methods to diagnose and subclassify patients presenting with dementia. Such tests may provide invaluable insights into the nature of the dementing process, and may even lead to the identification of traits or states that predict responsiveness to drug treatment. Importantly, the successful development and validation of such non-clinical methods will require their use in clinical trials.

### 4.2.2.(c). Ancillary subject characteristics.

It is important to collect and report information about study participants that might affect their response to treatment or the investigator's ability to assess their response. Thus, beyond the routine documentation concerning each subject's stage and severity of illness, it is important to provide information about a subject's use of prescription and non-prescription drugs, level of physical disability (e.g., impairments of hearing and vision, arthritis, etc.), and level of self care immediately preceeding entry to the study.

## *4.3. Dosing issues:*

### 4.3.1. Choosing the dose and dosing regimen to study:

The task of documenting the efficacy of a drug and developing a regimen for its safe administration is best undertaken with basic information about the drug's clinical pharmacology and ADME in hand (i.e., presumably some preliminary data will have been gained during Phase 1 clincial testing). Obviously, if a clinical experiment is to succeed, the experimental drug must be administered in a manner that allows plasma concentrations presumed necessary to produce a therapeutic effect to be achieved without undue degrees of toxicity and/or dysphoric effects. Clearly, knowledge of a drug's metabolism, systemic bioavailability, rate of elimination and the relationship between plasma drug concentrations and dysphoric and/or untoward pharmacologic effects is invaluable in determining how often a drug can and/or must be given.

### 4.3.2. Enhancing compliance:

Because poor compliance may lead to the loss of a potentially effective antidementia drug, every effort should be made to ensure that subjects and investigators comply fully with the dosing plan for the experiment. While good study protocols mandate routine checks on patient compliance (plasma or urine sampling, pill counts, etc.), it may also be helpful to take steps to enhance compliance before a trial is actually begun.

For example, both product formulations and dosing regimens should be designed with patient compliance in mind. The palatability (i.e., taste, appearance, smell, consistency) of the dosage form should be considered as well as its ease of its administration and consumption. The elderly individual, even if not demented, may be physically impaired to the extent that it becomes difficult for him or her to open a container of drugs. Similarly, visual impairments may make it impossible for many older patients to identify the contents of a container or follow the dosing recommendations written upon them. The timing and complexity of a regimen may also create difficulties, especially for those with emotional and physical impairments.

For these reasons, among others, experts urge that ambulatory patients living outside special care environments not be included in clinical trials unless they live with a

responsible caregiver who agrees to cooperate in the process of drug administration and patient monitoring.

In sum, it behooves those conducting clinical investigations enrolling the impaired elderly to pay careful attention to matters of compliance.

### *4.4. Efficacy assessment:*

#### 4.4.1. Prospective identification of major outcome assessment variables: the avoidance of multiplicity.

The protocol for every clinical study intended to serve as a source of 'substantial' evidence of efficacy should prospectively identify which outcome variables among the many assessed will be employed to evaluate the clinical investigation's overall outcome vis a vis the efficacy of the drug. Prospective designation of outcome variables is necessary to prevent the overall experiment's type I error rate from being grossly inflated over the nominal 'alpha' level at which each outcome variable assessed is tested.

However, this recommendation allows, provided that the designation is made prospectively, regulatory point is that the outcome variables must be specified before the experiment is analyzed, preferably before it is conducted. In no case, should the outcome measures be selected on the basis of an evaluation of the data developed in the study.

#### 4.4.2. Specific assessments required to document an 'Antidementia' claim:

To gain an antidementia indication for a product, a sponsor must provide substantial evidence that the product 1) has a clinically meaningful effect and 2) exerts its effect on the 'core' manifestations of dementia. This compound requirement can be met by showing, in more than one adequate and well controlled clinical investigation, that the drug product is superior to an appropriate control treatment on both 1) a global assessment performed by a skilled clinician and 2) a performance based, objective test instrument providing a comprehensive assessment of cognitive functions. The global assessment ensures that the effects detected are clinically meaningful; the

performance based assessment instrument ensures that the effect of the drug is upon the 'core' phenomena of dementia.

A compound requirement for establishing an antidementia claim is considered necessary to 1) preclude the approval of drug products that produce no clinically meaningful effects on the overall status (e.g., health, function, etc.) of demented patients, but do, because of their pharmacologic activity, cause detectable changes in patient performance on objective tests that are of uncertain clinical relevance, and 2) preclude the award of antidemential indications to drug products that exert a beneficial, but non-specific and/or pseudospecific effect on the overall clinical state of individuals who happen to be demented (e.g., effects on sleep, appetite, etc.).

The decision to use a combination of two different types of outcome assessment to evaluate the efficacy of antidementia drugs was made with the support of a number of experts working in the field of dementia and geriatrics24.

#### 4.4.3. The choice of the performance based comprehensive cognitive assessment instrument:

As noted, a definitive efficacy study intended to support an antidementia claim must employ an instrument that has a documented ability to detect changes in the core cognitive manifestations of dementia. Which instrument is used is not important so long as the one selected yields a performance based assessment. Preferably, the instrument chosen will have been successfully used in clinical studies with demented patients, and will be recognized as valid and reliable by a substantial proportion of experts in the fields of dementia and neuropsychological assessment. Examples of performance based assessments, that may be used include many of those identified as useful for assessing the severity of the dementing process (see Section 4.2.2.2).

The sensitivity of the instrument and the level of pathology it assesses should be matched to the severity of illness exhibited by the patients studied. In the absence of established effective treatments for dementia, the sensitivity of a rating scale to changes in the core phenomena of dementia can so far only be documented through repeated testing of cohorts of demented patients followed longitudinally. In any case, a rating scale selected for use in an efficacy study should ordinarily have been tested and evaluated in patients at several stages of the dementing process. Estimates of the

mean rate of deterioration as measured by the scale (and the variance associated with those estimates) in several samples of typical demented patients can be helpful in estimating the power of planned experiments. For example, for a drug that slows the rate of the dementing process, but does not cause improvement over baseline status, the expected maximum treatment effect is equal to the change in the average score attained on the instrument over an interval of time equal to the duration of the planned study.

### 4.4.4. Global assessments:

The clinician's global assessment serves as the primary measure of the clinical utility of a product's antidementia effect.

Global assessments offered by clinicians, however, have certain limitations and problems. The subsections that follow discuss the type, choice and use of global assessments ratings that can be made by clinicians.

#### 4.4.4.(a). Types of clinical globals and their general properties:

Two types of clinical global assessments are used commonly in clinical investigations as indicators of the overall status of patients.

One type, the 'clinical global improvement rating,' is designed to capture the extent of overall improvement or deterioration that the clinician perceives has occurred in the patient's status since an earlier evaluation (i.e., usually, a baseline evaluation).

The second type, the "absolute global severity assessment," is intended to capture the absolute severity of the medical condition affecting the patient. The degree of severity is judged in relation to the full range of pathology exhibited by patients suffering from the disease for which the experimental treatment is being evaluated.

Both types of global ratings rely heavily on a rater's clinical skills, training, and prior experience. The facets of patient behavior and appearance considered by a clinician formulating a global assessment are not ordinarily specified; indeed, the rater determines (consciously or unconsciously not only which attributes contribute but determines their relative importance to the assessment offered. Nothing prevents a

rater from focusing on different attributes or assigning different weights to attributes on different occasions.

Global scores, however, are often standardized; commonly, for example, a rater is only allowed a limited number of options for recording an assessment. Thus, the value of global rating might be limited to a fixed, small sequence of integers ordered along a dimension of increasing or decreasing severity/intensity (e.g., a 7 point global improvement scale might use 4 to represent no change, 1 to indicate marked improvement, and 7 to show marked deterioration, etc.)

While the use of a limited set of outcome categories reduces the range of numerical

ratings that the clinician can assign to a patient, there is no way, short of practical training, to control how different raters weigh and combine different aspects of the clinical picture in their ratings, or where, along the scale they locate various degrees of improvement or deterioration. Of the two types of globals, the one based on absolute severity of illness can be expected to exhibit greater inter-rater reliability. This is predicted by the nature of the tasks involved in making the two types of global assessment.

#### 4.4.4.(b). Contrasting properties of improvement and severity based global assessments

Absolute global severity ratings require a relatively skilled/trained clinician to assign a patient to a stage of illness ranging from very mild to very severe; however, the skills necessary to classify patients according to stage of illness can probably be taught with relative ease, especially if raters receive sufficient training (e.g., instruction, standard case vignettes, etc.) Training can usually be facilitated by providing examples of patients representative of each absolute severity category.

Global improvement ratings, based as they are upon a perceived degree of change in the clinical status of a patient's condition, pose additional problems, however.

To begin, because an improvement score represents a difference between two evaluations, a global improvement score is only valid if it is provided by a rater who sees the same patient on each and every occasion that a rating is made.

Global improvement assessments pose increased difficulties (relative to global severity assessments) in regard to the precision and consistency in which the value of the global assessment made maps to the size of the perceived clinical effect. The magnitude of the clinical pathology that can be mapped to any global assessment scale can be no greater than that between total well being and the most advanced state of the illness under treatment. When treatment is directed at a potentially totally reversible illness (e.g., depression), the maximum range of and potential change in pathology are identical and so, logically, are the representations of that change on either global serverity or global improvement assessments. However, in any condition where the extent of clinical improvement is modest (e.g., as in the treatment of dementia), the range of change in pathology evaluated is considerably smaller than the full range of pathology seen in the illness. As a result, the range of change in pathology mapped on the improvement global is narrow compared to that mapped by the absolute global. Put another way, clinicians asked to make an assessment of global improvement are regularly required to assign a set of ordered integers to a range of clinical change that may be no greater than that corresponding to a difference of one unit on the absolute global. It can be argued that this makes the global improvement potentially more sensitive to small clinical effects. On the other hand, it may make the global improvement far less reliable. The likelihood of lesser reliability is also predicted by the fact that it is exceedingly difficult to train raters in the use of an improvement scale where there is no or minimal opportunity to find examples of patients where improvement has been observed.

### 4.4.4.(c). Additional caveats concerning the use of globals

Irrespective of type, a number of caveats apply to the use of global assessments.

First, global ratings are only valid if raters are unware of treatment assignment. Beyond the usual precautions ordinarily taken to avoid 'blind breaking,' special efforts should be made to deny those making global ratings any clue to the nature of the treatment assignment. For example, access to information about untoward clinical responses reported by and/or abnormal laboratory test results obtained on the subjects being assessed should be blocked. If possible, those providing global assessments should be required to base their ratings on video-taped interviews presented in non chronological, permuted sequence.

Next, global assessments are intended to be based on clinical observations made personally by a clinician who has had adequate opportunity to sample the patient's behavior and appearance. In particular, a valid global assessment cannot be based on second hand reports, regardless of the alleged reliability of the primary source (e.g., verbal reports made to the clinician by nursing staff or family.)

### 4.4.4.(d). The choice of global assessments

Despite their limitations, global assessments are the ultimate test of the clinical utility of a drug's antidementia effects. Consequently, a global assessment is required in every clinical investigation intended to provide substantial evidence of an antidementia drug's efficacy.

The question remains, however, as to which global is to be preferred.

The discussion to this point would seem, on face, to favor the use of the global that captures the absolute severity of pathology observed. There is, however, no consensus on this point. In fact, despite its seeming advantages (e.g., presumed greater interrater reliability, relative ease of learning, etc.) some experts are concerned that absolute severity assessments will regularly fail to detect (i.e. be insensitive to) the modest antidementia effects that can reasonably be expected to be produced by investigational drugs of the type now in development, at least over the relatively short periods (e.g., a few weeks or months) that correspond to the duration of a typical clinical trial. Recall, that if a drug totally stops the progression of dementia, its observed treatment-effect can be no greater than the average change in pathology observed in untreated demented patients over an interval of time equal to the duration of the study. of course, if a study is long enough, an absolute global will be more than adequate to detect between treatment differences in outcome.

In sum, it is not possible at this time to endorse one of the two types of global assessment in preference to the other. Either or both can be used. However, if both are used, the protocol for the study should specify which of the two globals will be considered the primary measure for evaluating the efficacy of the drug (i.e., the global to be used in tandem with the comprehensive performance based cognitive assessment instrument).

### *4.5. Safety Assessment.*

Although the traditional goal of phase 2 is to document the efficacy of a drug, phase 2 clinical trials often provide a large proportion, if not the bulk, of information relevant to the assessment of a drug's safety. In particular, the randomized controlled trials of phase 2 often provide the only source of information that can be used to determine the 'attributable' risk of drug for events seen spontaneously in the population being treated. Thus, comparative safety information collected in phase 2 can be extremely important, if not critical, to the approval decision affecting an antidementia drug.

In general, every participant in a phase 2 study should be evaluated at or immediately before, exposure to drug or control treatment begins. This baseline information is critical to

determining, if an abnormality is detected, whether it is reasonably attributable to exposure to the assigned treatment. Evaluations should then be conducted at reasonable intervals throughout the period of exposure to treatment and during the period immediately following drug discontinuation. The latter period may be the only source of information about withdrawal emergent adverse events.

Ordinarily, every patient should undergo a comprehensive physical and neurological examination and have a battery of laboratory and special tests performed. For example, blood chemistries (electrolytes, liver function tests, etc.), blood counts, differentials, urine analyses, stool for occult blood, and EKGs are the minimum acceptable set of tests that should be performed before, during and after exposure to the investigational agents.

The goal of the assessment is to document that the patient suffered no ill effect during exposure. Should any abnormality occur, additional testing, including obtaining samples of plasma for assay for drug concentration, full follow-up and appropriate medical intervention is essential.

### *4.6. The required duration of Phase 2 studies:*

One of the more vexing questions affecting the development of all drug products involves the duration of the clinical trials that will be accepted as valid sources of

substantial evidence of efficacy. For drugs that are used to treat acute, transient illness, there is not much of a problem; the drug is evaluated for at least as long as it likely to be used to produce its desired effect. For example, an injectable analgesic, intended to be used for one or two days

in most cases, might be evaluated in efficacy studies lasting as long as several days to a week.

Drugs intended for palliation of chronic illness, however, pose an entirely different set of considerations. Ideally, the efficacy of such products ought to be demonstrated over the full interval of their probable duration of use once they are marketed. However, practical considerations have made this goal regularly unattainable. Antidepressants, drugs that are routinely administered for periods of 6 months to 2 years in the management of an episode of depression, for example, are evaluated for efficacy in studies lasting but 4 to 8 weeks.

Understandably, therefore, it is impossible to specify precisely how long a drug product for which an antidementia claim will be sought should be evaluated.

In the abstract, it seems easy to argue the principle that longer studies will be more representative of the actual conditions under which an antidementia drug will be used. Moreover, as noted earlier, if a treatment merely retards the rate of functional deterioration on the 'core' manifestation of dementia, the size of the average treatment effect will be a direct function of the duration of the study. Under such circumstances, a statistically significant effect, on a performance measure or a global might be found after a 6 month long, but not after a 3 month long, study.

However, factors favoring shorter studies must also be considered. Patient recruitment for a very long study may be quite difficult. Patients willing to accept randomization to a less promising treatment for a matter of weeks may balk at participating in an experiment that may prevent their gaining access to an active, albeit only putatively effective, treatment for six months. Moreover, the longer the duration of a study, the smaller the proportion of subjects randomized that are likely to complete the study as planned, an outcome that invariably complicates the study's ultimate analysis.

At the time this manuscript is being written (circa 1990), therefore, it is not possible to make a specific recommendation regarding duration of treatment. It seems unlikely, however, that experts will judge studies of less than 3 months adequate to support an antidementia claim.

# 5. Phase 3

## *5.1. Overall goals of Phase 3:*

Phase 3 is envisioned as a period of expanded testing during which a product whose efficacy has been established definitively in rigorously controlled phase 2 studies is evaluated under conditions more typical of those likely to prevail once the product is marketed. Phase 3 is intended to confirm efficacy, identify risks, and develop directions for use that include advice for dealing with common adverse consequences associated with the use of the drug. it is during phase 3 that experience is gained with the drug in vulnerable populations, 25 populations that could not ordinarily be identified on theoretical biological or physiological grounds. Phase 3 ordinarily provides the bulk of the evidence upon which the warnings and precautions about the use of the drug are based when it is first marketed. Critically, phase 3 is ordinarily the chief source of the evidence of 'safe passage' that is used to set upper limits for catastrophic risks not seen during the testing of the drug26 .

## *5.2. The scope of Phase 3: numbers of patients*

The value of a drug development program increases in direct proportion to the extent and scope of the drug's evaluation. Obviously, the warrant of safety and knowledge about the drug increases with the number of patients studied and with the variation and nature of the conditions under which clinical testing is carried out.

In regard to the absolute size of a development program, it is impossible to state precisely what minimum number of patients must be studied before an NDA for an antidementia drug will be approved27 , but, at a minimum, at least a 1000 patients should be exposed for a minimum of several weeks to doses within the range to be recommended in labeling; of these patients, perhaps a third or more (e.g., 300 or so) should have been on doses of the drug at or above the median recommended dose for

a period of 6 months to a year. Importantly, these are minimum estimates and may not suffice if any specific safety problem is identified. In any case, the total drug development cohort includes all patients studied in all drug development phases. Accordingly, therefore, the scope of Phase 3 is affected by the scope and extent of prior phases and the evidence of developed in them.

## *5.3. Outcome assessment in Phase 3*

### 5.3.1. Routine safety assessments

Although the number and kind of observations made on individual patients in phase 3 is generally less than in phase 2, patients in phase 3 trials should regularly undergo comprehensive medical (including routine blood chemistries, urine analyses, CBCs and EKGS), neurological, and behavioral assessments immediately prior to drug exposure and periodically thereafter throughout the course of their treatment. In addition, other outcome assessments may be required; however, the precise nature of these additional assessments will vary with the purpose of each study.

### 5.3.2. Pharmacokinetic screening

Phase 3 chronic studies provide an opportunity to collect information that may be useful in identifying causal associations between pharmacokinetic and untoward clinical phenomena. Plasma samples obtained from patients exposed chronically to a new drug may also help identify factors contributing to the variability of a drug's pharmacokinetic performance within the population. Thus, the collection of two or more samples of blood from patients at know times following drug administration who are on stable dosing regimens is encouraged in every phase III trial.

### 5.3.3. Patient selection

There should be few restrictions on the nature of the patients entering phase 3 clinical trials. In general, any patient, regardless of age, sex, concomitant illness or concomitant drug use, should be admitted to a phase 3 study if treatment with the drug is appropriate and the patient suffers from dementia. Put another way, if a demented patient would be likely to receive treatment with the drug if it were marketed, the patient should be considered appropriate for entry into a phase 3 trial.

Sponsors may tend to resist this recommendation, believing, not irrationally, that untoward events arising spontaneously from such 'high risk' patients will be erroneously attributed to the action of their drug. This is certainly a risk, but it must be taken if a fair estimate of the risks associated with the use of the drug are to be gained.

### *5.4. Special design issues in Phase 3 Safety studies:*

#### 5.4.1. Protecting a drug's reputation: controlled safety assessment studies:

One protection, at least against a false implication that an investigational drug causes common adverse events that, in truth, are arising spontaneously from a high risk population, is to assign such advanced, 'high risk' patients randomly to the new drug and a suitable inactive or minimally active control treatment, the latter providing a means to estimate the spontaneous incidence of adverse events occurring in the population being tested.

A major drawback to this suggestion is the difficulty of finding a control treatment that will be acceptable to patients seeking access to new, presumably promising, investigational agents. So long as legitimate doubt exists about the net value of the investigational agent, there is no moral dilemma involved in asking a patient to accept randomization to a treatment that may be inert or marginally useful and known to be relatively innocuous. Of course, the question remains whether it would be possible to recruit sufficient patients to carry out such a study; clearly, the incentives for a patient with a progressive and irreversible illness to participate in any long term study in which there is a chance of randomization to an ineffective or marginally effective treatment are few, if any, if he or she believes that effective or potentially more effective (compared to the control) treatments exist.

Of course, once an effective treatment28 for dementia is found, long term placebo controlled trials cannot be justified. However, once such a treatment is found, it will be an ideal control for the evaluation of the relative safety, of other new drugs.

This discussion illustrates the importance of obtaining as much valid information as possible from each clinical experiment. For example, if a comparatively large number of patients have been studied in controlled trials during phase 2, the implications of a

high incidence of untoward events observed among 'high risk' patients being followed in phase 3 trials that do not employ a control may not be so critical to a drug's image; that is, there will be at least some evidence to support the argument that the increased incidence of untoward events is a function of the patients studied and not the drug. However, this argument is not entirely persuasive; an interaction between the drug and the 'high risk' status of the phase 3 patients may also account for the increased incidence, a point that will have to be emphasized in product labeling should the drug be approved for marketing.

It is also important to acknowledge that a control group provides few protections against serious and/or catastrophic events that occur spontaneously at low frequencies. For example, if only one or two catastrophic events are observed and each has occurred in a drug exposed patient, the evidence of causal association will be weak, but will, nonetheless, have to be emphasized in product labeling, especially if drug exposure is a reasonably plausible explanation for the event.

### 5.4.2. Directions for use

Efficacy in sustained use Phase 3 clinical testing provides an opportunity to develop information that will enhance the quality of directions that can be written to guide the prescriber in using a drug prudently and safely.

Although it is not critical to approval, information about the duration of a drug's efficacy in sustained use and the consequences of its withdrawal after chronic administration is always valuable. Accordingly, an uncontrolled study intended to assess the safety of a drug in chronic use may be modified in a manner that provides for a phase during which patients can be withdrawn from treatment and re-randomized to the treatment to which they were originally assigned or a suitable control (e.g., placebo).

If there is no difference in the behavior of the groups created following their rerandomization, questions must obviously be raised about the efficacy of the drug in extended use. On the other hand, if clinical deterioration is seen only in the control group, it is evidence that the drug is exerting some sustained pharmacological action. Importantly, however, it is not safe to assume that the drug is actually exerting a beneficial therapeutic effect; the deterioration observed may only be a sign of

physiologic dependence, the clinical findings merely manifestations of a withdrawal reaction. Clearly, whatever the interpretation, a change in status following blinded withdrawal and rerandomization is information that can help the prescriber in the management of patients, and, therefore, important to describe in labeling.

## 6. The importance of labeling

Ultimately, the approval of a new drug for marketing rests on a judgment by the review team that the evidence submitted to the NDA documents that the drug is safe 'for use' and 'effective in use,' under the conditions of use recommended in its proposed labeling. Consequently, one useful measure of the comprehensiveness

of a development program is the extent to which the information generated by it will support drafting of product labeling. In general, if a sponsor can draft authoritative labeling as required in 21 CFR 201.57, supporting the statements made in each of the prescribed sections with evidence supporting the statements made in each it is likely that the drug development program is reasonably complete. In contrast, if evidence to support labeling statements is unavailable, if attempts to draft labeling require sanguine assumptions and appeals to biologic plausibility, the drug has almost certainly not been adequately evaluated.

### *6.1. Meeting with agency staff*

Guidelines provide only general advice about the development of a drug. Accordingly, sponsors are encouraged to consult agency staff periodically. Meetings are ordinarily arranged at the end of Phase 2 and before the submission of NDAS, and for Subpart E drugs, may be held prior to Phase '2 and before IND submissions. Moreover, regardless of the time at which they arise, important issues affecting a drug's development should be communicated to the FDA. Matters of safety must be communicated rapidly and quickly as dictated by regulation. Matters affecting clinical designs and overall development strategy, however, should also be communicated.

If needed, ad hoc telephone conferences and face to face meetings can be arranged, resources and time permitting

## 7. Practical advice on filing an IND

Clinical research with investigational New Drugs must be conducted under appropriately authorized Investigational New Drug Applications (INDs). To obtain an IND, the prospective sponsor must submit documentation including a completed form 1571.

In effect, the form 1571 constitutes the sponsor's promise to abide by all rules and regulations pertaining to the use of investigational agents. Detailed instructions about how to file for an IND for the study of an antidementia agent may be obtained by writing to the appropriate Drug Group29. However, the following provide a useful introduction into two preclinical areas that affect a sponsor's ability to initiate clinical testing

### *7.1. Product Identity, Strength, Purity, controls, and Stability:*

Before any clinical study can begin, basic information must be provided to the agency about the drug product that sponsor proposes to administer in clinical studies. An IND is ordinarily granted for a particular formulation of a drug substance. Thus, if a sponsor wishes to use another alternative formulation of the drug substance, he or she must ordinarily seek and gain agency permission for modifying the product before administering it to patients. Thus, it is prudent for sponsors to obtain adequate supplies of a particular formulation from an approved source prior to initiating any studies.

If this precaution is not taken, it may become necessary to suspend a clinical trial if supplies run out and an alternative acceptable supplier for the drug product cannot be found. The sponsor should not assume that an alternative formulation may be substituted willy nilly; a different source of a nominally identical drug product may, in fact, be substantively different. As with other IND requirements, the scope, detail and depth of information and documentation needed about a drug product will vary with the proposed extent and duration of its use and the nature of the formulation being employed. For example, much more information about slow release products may be required than about a lyophilized-powder supplied in a sterile ampule-that is reconstituted with sterile saline prior to injection. The reason, of course, is that the

risks associated with the use of a poor slow release product may be much greater than those involving an immediate release one. In particular, the slow release formulation may 'dose-dump' and cause inadvertent overdose of the patient. Applicants unfamiliar with the basic requirements for the submission of the chemistry portions of an IND should refer to :

### *7.2. Preclinical toxicology:*

The preclinical toxicological tests required for an IND are adjusted to reflect the extent, duration and proposed use of the product and the current phase of its development. Ordinarily, far less information is required for initiation of phase 1 than for Phase 3. However, even Phase 1 human studies may not ordinarily take place until there is information about the acute risks of the product in at least two animals species.

In addition to tests intended to document that the drug will not kill within minutes to hours of its administration at doses anywhere close to those that will be administered to humans, acute toxicity testing in two species of animals at doses ranging from 10 to 100 fold that to be administered to man should be conducted to gain some insight into the likely toxicity of the drug and the margin of safety that may be involved.

Ordinarily, toxicity testing is conducted by the same route as that to be used in humans. The extent of toxicity testing required will vary from the minimum just described (used for an injectable that will be given at most for a few doses over a period of a day or two) to a full panoply of tests including 1 year chronic toxicity testing in two species, in-vivo life time carcinogenicity testing in two species and, special

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