NAVIGATING CHALLENGES IN ALZHEIMER’S DISEASE DRUG DEVELOPMENT

REGULATORY CONSIDERATIONS FROM AN INDUSTRY PERSPECTIVE

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INTRODUCTION

Alzheimer’s disease (AD) is by far the most common dementia in later life, and its immense impact from the individual to an international level is well recognized (Alzheimer’s Disease International 2015). Globally, the number of persons age 65 and older living with AD is projected to increase from close to 47 million in 2015 to 135 million in 2050 (Alzheimer’s Association 2015).

While the pathophysiology of AD is not fully understood, amyloid plaques and tau tangles are considered hallmarks of AD (Hyman 2012); neuroinflammation also appears to play a role. A cholinergic deficit is a key characteristic of the disease. Symptomatic presentation of the disease begins some one to two decades after disease initiation. Although AD is one continuous, gradually progressive disorder, it is often classified into stages (Albert 2011; McKhann 2011; Sperling 2011; Dubois 2009):

- **Preclinical AD**: Biomarker evidence of AD pathology, but clinically normal
- **Prodromal AD (or mild cognitive impairment due to AD)**: Biomarker evidence and cognitive symptoms with no or only subtle changes in function
- **Mild AD dementia**: Cognition continues to worsen, daily function begins to be impaired
- **Moderate AD dementia**: Cognition and function are more impaired and patient safety becomes a greater concern
- **Severe AD dementia**: Loss of most or all of ability to independently care for self

Initial efforts in development of AD treatments focused on the most clinically-evident stages of AD (mild-to-moderate and severe AD dementia). Our understanding of the disease has increased considerably in recent years and there is general alignment in the AD field on the importance of developing treatments that can address the disease at earlier stages, to prevent or slow progression from preclinical to symptomatic stages as well as from early to later stages of dementia – if successful, those treatments would significantly limit future impacts on society. The demand for symptomatic treatments and treatments that address specific behavioral and psychiatric symptoms of dementia remains a critical need for the 46.8 million people with dementia. Additionally, there is increasing attention on intervention earlier in AD continuum using potential disease-modifying therapies (DMTs) that target the underlying pathophysiology of AD. The hope is that a combination of DMTs and new symptomatic/neurotransmitter agents will fundamentally change the face of the disease and will allow AD to be treated similarly to other chronic conditions—that is, using combinations of medications with different mechanisms of action to allow patients to maintain cognition and function for a longer portion of their lifetime.

Aspirationally, not unlike HIV/AIDS, one might be ‘amyloid positive’ but not experience the full-blown symptomatic stage of the disease.

Challenges to efficient and successful AD drug development and early treatment are many. The disease has a multifactorial etiology, a complex pathophysiology, and progresses slowly. In the clinical trial environment, challenges exist because overt clinical symptoms are not evident until considerable change has occurred within the brain; the most appropriate outcome measures in early AD have not been widely agreed upon; there are no surrogate biomarkers currently available; there is difficulty activating and coordinating clinical trial sites globally; and strategies for identifying, recruiting and retaining trial participants are time- and cost-intensive. The dearth of approved AD therapies highlights some of these challenges; no new treatments have been approved since memantine, more than 10 years ago.

Global leaders have set an aspirational goal of 2025 for finding an effective way to treat or prevent AD (NAPA 2011, Vradenburg 2015). Recent analysis by ResearchersAgainstAlzheimer’s, a global coalition of over 400 leading researchers, determined that 17 drugs in Phase 3 have the potential to reach the market in the next 5 years (UsAgainstAlzheimer’s 2016). Given the near-term prospects for innovative therapies, it is important that governments, health care providers, regulators, payers, and society are prepared to provide appropriate access to therapies which are proven to be safe, effective and useful. All stakeholders play a central role in finding ways to overcome key challenges in bringing new AD drugs to the patient. Regulators have shown great willingness to engage in inter-agency dialogue and to consider, as well as put forward, potential innovative solutions.

In this paper, we discuss some of the key challenges of AD drug development that are pertinent to the regulatory environment and highlight regulatory activities that have been and are being put in place to address these challenges. We also propose further steps that regulators might consider to help overcome current and potential future obstacles in AD drug development, including development of additional guidance more specifically focused on recognized challenges related to trial design, endpoint selection and statistical analysis. This document focuses specifically on treatment of AD rather than dementia in general, though learnings from AD drug development are likely to aid development of treatments for other dementias. The document is not intended to be all-encompassing, but rather focus on some specific areas of importance in the current environment.
A PATH TO MORE EFFICIENT AD DRUG DEVELOPMENT

TRIAL CONDUCT
Key to success in the clinical trial environment is ensuring that trials provide clinically meaningful information that is appropriate to the indication. This may include cognitive, functional, and/or behavioral effects.

Cognitive decline is the initial symptom of AD and drives later functional decline; showing cognitive benefit with a DMT or symptomatic AD treatment is essential. For symptomatic AD treatments, benefit would be considered cognitive improvement from baseline, with onset over the initial weeks or months of treatment. In addition, symptomatic agents, through improvement over baseline, may allow patients to maintain cognitive ability for longer at their current stage of disease. For a DMT, cognitive benefit would be evident later, manifesting as a slowing in rate of decline rather than improvement from baseline. In clinical trials, DMTs should also show treatment effect building over time of treatment, persistence of effect, or biomarker evidence of effect on disease pathophysiology. For treatments targeting behavioral, psychiatric or other symptoms, in addition to demonstrating an improvement in the targeted behavioral or symptoms, ruling out a negative impact on cognition is needed.

Trial design, statistical analyses and clinical endpoints all play a key role in the evaluation of potential new treatments for AD.

TRIAL DESIGN AND STATISTICAL ANALYSES
The slowly progressive nature of AD requires large trials of long duration in order to show any evidence of a treatment effect. To increase efficiency in AD drug development, there has been a need to consider alternatives to traditional individual Phase 1, 2, and 3 trials. Regulators have shown flexibility and openness to innovative trial designs; specific examples are discussed here:

Adaptive trials make use of interim study findings to modify various aspects of the study, thus improving efficiency (e.g., smaller sample size requirement, shorter overall development time). They may be helpful both earlier in clinical development (exploratory studies) and later (Phase 2/3 efficacy studies). Both FDA and EMA have provided helpful general guidance on adaptive design (FDA 2010, EMA 2007) and adaptive trial designs have been effectively used, for example in oncology and diabetes. In the AD field, challenges exist with adaptive design, in part because of the absence of surrogate biomarkers or other early indicators of efficacy. Both agencies have been open to considering adaptive design in AD drug development, however, and there are several Phase 2/3 adaptive studies in AD currently ongoing (e.g., NCT02245737, NCT01739348, NCT02569398 [see clinicaltrials.gov]). Due to the lack of surrogate markers, adaptive AD trials typically adapt based on safety and tolerability rather than efficacy.

A randomized start or delayed-start design (Leber 1997, Liu Seifert 2015) has been proposed as a possible strategy to demonstrate a disease-modifying effect—that is, an effect on the underlying disease pathophysiology with increasing benefit over time and persistence of effect. Briefly, the design comprises a placebo-controlled period during which participants are randomized to either an active treatment or placebo, followed by a delayed-start period in which those participants originally assigned placebo are switched to active treatment (delayed-start participants) and those originally assigned active treatment continue on this treatment (early-start participants). If the active drug has a purely symptomatic effect, a delay in administration should have no lasting effect and the delayed-start participants are expected to “catch up” to early-start patients in terms of magnitude of effect. If the active drug has altered the underlying disease process, the delayed-start participants will not overcome the losses sustained during the delay and will not “catch up.” The application of a delayed-start design has been limited due to operational challenges, as well as the absence of a robust statistical method for the analysis. Recently, Liu-Seifert et al. (2015) proposed a method of delayed-start analysis to better ascertain possible disease-modifying effects of treatments in AD. Briefly, they used a modeling approach and test procedure to assess the hypothesis of non-inferiority, comparing the treatment difference from the beginning to the end of the placebo-controlled period with the difference at the end of the delayed-start period. The proposed non-inferiority method for delayed-start analysis controls Type I error and addresses some of the challenges posed by previous approaches.

FDA and EMA are accepting of a delayed-start trial design as supportive for disease modification (EMA 2016, FDA 2013). While it has not been used in an AD regulatory submission to date, multiple sponsors are using the delayed-start design in Phase 3 AD studies. As yet, there is no consensus on the most appropriate statistical methods to employ.

Once a DMT is approved, there may be a need to consider active comparator studies—either a superiority or non-inferiority trial, with or without a placebo arm. If a DMT becomes part of standard-of-care, non-inferiority trials with the DMT as the active control treatment and without a placebo arm may be considered most appropriate from an ethical standpoint. Both FDA and EMA
have provided general guidance on non-inferiority trials (FDA 2010b, EMA 2000, EMA 2005). While there are differences between the FDA and EMA guidance on non-inferiority trials, both agencies agree that it is critical to pre-specify an appropriate non-inferiority margin that is based on both statistical reasoning and clinical judgment. Both also agree that this often is a difficult task and requires thoughtful consideration. Harmonized guidance regarding non-inferiority trials in general would be helpful, as would more specific guidelines tailored towards AD trials.

Given the complex pathophysiology of AD, it is recognized that combination therapy may be necessary for optimal treatment. Challenges in combination therapy development are numerous and this topic is well reviewed by Hendrix et al. (2016). Traditionally, for study of novel-novel combination treatments, factorial trial designs have been recommended. They permit assessment of both individual treatments and the interaction between treatments to determine if there are synergistic or additive effects. In its simplest form (2x2 factorial design), two active treatments are tested in a 4-arm study: placebo, active treatment A alone, active treatment B alone and a combination of A and B. Factorial studies are large, expensive and challenging in terms of dose selection. FDA provides high-level guidance on this topic (FDA 2013b). For Phase 2, a factorial design is recommended, but FDA has expressed openness to consider other options instead of a full factorial design in some circumstances; Phase 3 design is evaluated on a case-by-case basis. Recent EMA AD draft guidance (EMA 2016) acknowledges the challenges with factorial design and, like FDA, takes a somewhat open view on the topic. Further discussion by regulators and communication of possible options for AD studies would be welcomed.

Overall, despite the availability of general guidance in terms of trial design and analyses, opportunities still exist for further discussion and guidance:

- There has been a great deal of interest among statisticians across industry and academia in collaborating and forming a pre-competitive research working group to address the critical methodology needs in the AD field; this AD statistical consortium could be a partnership with regulatory agencies, including FDA and EMA, to develop AD specific guidelines, for example for non-inferiority trials, adaptive design, and novel-novel combination trials.
- While EMA is very open to considering innovative trial design in general, the implementation of these studies at the national level can be more challenging, with authorization of clinical trial applications being the responsibility of each member state where the trial is taking place. A broader understanding and acceptance of innovative designs across member states would be helpful and the upcoming Clinical Trial Regulation will help to ensure consistency of decision making: CHMP/EMA could play a key role in disseminating the acceptability of novel trial designs.

CLINICAL ENDPOINTS

In terms of endpoint selection, there has been much discussion over what is appropriate, particularly with regards to whether trials in early AD need to rely on both cognitive and functional primary endpoints. Cognitive decline precedes, and predicts, functional decline in the natural course of the disease (Zahodne 2013, Liu Seifert 2015), and in populations earlier in the disease continuum (prodromal AD, mild AD dementia, for example) less functional impairment may be evident or treatment effects on function may be more difficult to detect (Siemert 2016), at least using currently-available tools. As a result, it may be most appropriate to place more focus on cognition in the study of interventions in these early AD populations.

Selecting appropriate functional endpoints for the study of early AD populations remains challenging because there is neither full understanding nor agreement on the most appropriate measures to use. At this time, it may be most appropriate to include multiple functional measures in a study and consider study results in a more holistic manner using a weight of evidence approach, in a similar manner to that accepted by regulators for evaluating treatment effect using biomarkers (i.e., not requiring those endpoints to be included in a statistical hierarchy, provided there is a pre-specified analysis plan for each). Instrumental activities of daily living (ADLs) are more relevant for functional assessment earlier in the clinically-evident stages of the disease, as they require higher cognitive processes than basic ADLs.

In general, there is need for more specific and sensitive clinical tools for assessing both cognition and function. Composite endpoints, which capture those components from existing scales that have the ability to discern decline in early AD populations, are also likely to prove increasingly helpful.

Regulators are recognizing some of these challenges outlined above, and taking action accordingly. FDA is accepting of a cognitive endpoint as the sole primary endpoint in studies of preclinical AD populations, and a composite of cognition and function in studies of prodromal AD populations (FDA 2013). Given the overlap between prodromal and mild AD dementia, and the use of combined prodromal and mild AD dementia populations for several clinical trials (termed “early AD” populations), it would be appropriate to include mild AD dementia as part of the guidance for early AD trials and consider accepting similar primary endpoint options.
To progress effectively in this area, there is a need for regulators to maintain or establish dialogue with those developing new tools as well as with patient groups to determine important components of clinical meaningfulness of new tools. FDA recognizes that patient perspective is critical in helping to understand the context in which regulatory decisions are made for new drugs and is working to more systematically obtain the patient perspective on specific diseases and their treatments (FDA 2013, 2015). EMA is also interested in including the patient’s perspective in the regulatory process.

**REGISTRATION STUDIES**

While approvals in the CNS therapeutic area have typically required two pivotal studies, approval based on findings from a single pivotal trial in AD can also be appropriate, particularly in light of the large sample size and study length requirements and the low likelihood of a placebo effect. Regulators appear to be open to considering a single pivotal study for AD, if results are robust and supportive evidence is provided. A single pivotal trial could enroll a population with earlier stage disease (e.g., prodromal AD) progressing to a later stage (mild AD dementia), such that two stages of disease are studied in one trial. Approval pathways that allow two pivotal studies to use two different populations in the AD continuum (e.g., one study for mild AD dementia and one study for prodromal AD rather than two trials for each) are also being considered by regulators.

Draft EMA guidance indicates the possibility of regulatory approval based on data from a single pivotal study (EMA 2016), if participants are followed up for a sufficient time to inform efficacy and safety in the subsequent stage; EMA offers more specific guidance on flexibility in pivotal trials for AD treatments. Guidance from FDA and other regulators on pivotal trial options such as these would be helpful.

**REGULATORY REVIEW PROCESS**

Regulators have made great effort to reduce the duration of marketing application review for treatments for serious diseases. In addition to reauthorization of the Prescription Drug User Fee Act in 2012 (PDUFA V), FDA has introduced expedited programs for treatments that address high unmet medical need—Accelerated Approval, Priority Review, Fast Track Designation, and Breakthrough Therapy Designation. EMA have revised their guidelines on the implementation of accelerated assessment and conditional marketing authorization to accelerate access to medicines that address unmet medical needs (EMA 2015), and introduced PRIME (EMA 2016b), a scheme that provides enhanced regulatory and scientific support for high priority medicines through advice at key milestones in development. In Japan, PMDA has begun reviewing requests for designation under the new sakigake early access pathway that could cut approval times for innovative therapies in half. Such steps to expedite review are commendable, and it is hoped that other regulatory agencies will follow suit.
RECOMMENDATIONS

Regulators are part of the rapidly changing AD clinical trial environment and can play an important role in providing clarity and continued responsiveness to the challenges in this area. Already, regulators have put in place innovative programs and are continuing to develop their views and guidance based on developments in the AD research field. We are confident that the efforts will build, with the 2025 goal in mind.

Given the evolving environment and the different mechanisms of action of drugs necessitating different study designs, endpoints and analyses, it is hoped that regulatory agencies will, at this stage, maintain flexibility in guidance. It is acknowledged that differences in regulatory views exist (e.g., as a result of cultural differences). However, harmonization is encouraged in those areas where it could reduce unnecessary burden. Cross-agency regulator meetings, such as the current gathering, are an important step; it would perhaps be helpful if regulators took further steps in publicly sharing their views on new scientific developments and continued to facilitate dialogue among agencies if discordance exists, to encourage understanding on all sides. This would help industry to identify future potential challenges and permit consideration of all regulatory viewpoints and their reasoning to assist decision-making. Collaborative efforts across academia, industry and regulators have also been productive, including the Lausanne Dialogues and Critical Path Institute’s Coalition Against Major Disease (CAMD); these types of collaborations will continue to be critical in stimulating dialogue between key stakeholders and prompting action.

As described earlier, specific areas in which increased regulatory focus could assist with more efficient drug development to reach the 2025 goal include:

1. Development of AD-specific guidance on inferiority/superiority trials for implementation when one or more DMTs are approved

2. Further evaluation of cognition as a primary endpoint option and a more pragmatic approach on how functional endpoints are evaluated early in the disease continuum (mild AD dementia and earlier)

3. Regulatory alignment on expectations for novel endpoints (composites and new functional and cognitive endpoints)

4. Regulatory alignment on delayed start analyses

5. Alignment in guidance from FDA and other agencies with that from EMA with respect to AD registration pathways (i.e., pivotal trial options)

Much will be learned from the data acquired during trials of the several potential AD treatments that are now in late-stage development. The trial results, along with continued dialogue amongst all stakeholders, will make important contributions to further advancing the fields of AD research and regulatory science.
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