Progress and Challenges in Alzheimer's Disease Drug Development: An Update on Scientific, Clinical, and Regulatory Considerations from an Industry Perspective

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INTRODUCTION
Alzheimer’s disease (AD) is by far the most common cause of dementia in later life, with wide-ranging impacts on individuals and on society (Alzheimer’s Disease International 2016). The burden is substantial. In the United States alone, 5.4 million Americans live with this disease, every 66 seconds someone new is diagnosed with it, and in 2016 Alzheimer’s-related costs accounted for $236 billion – nearly $1 of every $5 Medicare spends (Alzheimer’s Association - 2016 Facts). Globally, the number of people age 65 and older living with AD is projected to increase from close to 47 million in 2015 to 131.5 million in 2050 (Alzheimer’s Association 2016). When expanded to a global perspective, the economic, social, and emotional burden becomes even more urgent. Left unaddressed, AD alone will exhaust the healthcare budgets of many countries.

In 2016, a patient-led industry coalition submitted a paper to the OECD on navigating challenges in Alzheimer’s disease drug development. Despite tremendous research efforts and the steady work of regulators, most of the challenges and the recommendations identified in 2016 remain relevant, and some even more urgent, today. This paper now supplements and updates that earlier paper by highlighting recent developments in clinical trials, offering a perspective on how research into AD has shifted, and concluding with additional recommendations that regulators may consider in addressing these challenges. It is our hope that this paper, like that in 2016, will present fresh opportunities for further dialogue among all stakeholders involved in AD.

The etiology of AD remains tantalizingly elusive. Efforts to find a simple cause have been frustrated. Amyloid plaques and tau tangles are considered hallmarks of AD (Hyman 2012), and neuroinflammation and genetics also appears to play a role. The disease begins, and can be detected, ten to twenty years before symptoms generally present themselves. It is often classified into specific stages (Albert 2011; McKhann 2011; Sperling 2011; Dubois 2009) but is actually a continuum with overlap between different “stages,” such as prodromal and mild AD dementia. Clinical trials are often conducted in a population that includes adjoining stages of AD because there is overlap between them. For instance, several studies include an "early AD" population,
defined as prodromal AD/MCI due to AD plus mild AD. Recognizing this continuum, including with respect to studies involving an “early AD” population, has implications not only in the field but for regulators as well, for the approval of AD treatments for use in populations in the disease continuum.

A further challenge is the diversity of the descriptions of AD generated by the evolution of scientific advances and diagnostic systems. Divergent meanings are now imputed to “Alzheimer’s Disease”; for instance, the same stage can be termed “prodromal,” “amnestic MCI,” “predementia,” or “MCI due to AD”; similarly, treatment can be “AD secondary prevention” or “treatment of preclinical disease.” Alignment on a common lexicon for use in clinical settings would broaden discussion and understanding of the disease and its stages and reduce uncertainty in drug development.

Numerous distinctive characteristics of AD present unique challenges to successful development of drugs, some of which this paper will discuss. As we noted in 2016, global leaders have set an aspirational goal of 2025 for finding an effective way to treat or prevent AD (NAPA 2011, Vradenburg 2015). Given the increasingly significant burden that AD poses to governments, families, and patients themselves, the need for new safe and effective therapies developed in a timely and efficient manner is critical. Regulators play an important role in this effort through their openness to potential innovative solutions to address the challenges in AD research and development.

Clinical trials update: both disappointing and encouraging results

As discussed at the 2017 Lausanne IV conference on “Building the Ecosystem for Alzheimer’s Innovation,” the late-stage drug pipeline for AD continues to grow, with 58 drugs in Phase 2 trials and 32 in Phase 3; there are 76 trials in the Asia-Pacific region, and 162 in the US (Morgan 2017, Lim 2017). There are 77 drugs with a potential to have Phase 3 results available by the 2025 goal; if even a small number were to reach the market, this would radically change treatment of this devastating disease. A majority of these drugs are potential disease modifying therapies (DMTs). Research emphasis in DMTs has started moving beyond amyloid and tau to areas such as inflammation, neurotransmission, neuronal synaptic growth, and others. At the same time, a number of challenges to AD drug development have also been noted (Morgan 2017), including the slow pace of trial enrollment, the need for combination therapies (a similar challenge to developing drugs for AIDS, cancer, and heart disease), and diagnoses that often occur too late to enroll potential patients in trials.

Unfortunately, since the 2016 paper, there have been disappointing results in trials in mild-to-moderate Alzheimer’s disease, with unfavorable clinical results accompanied by variable biomarker outcomes. These included negative Phase 3 outcomes in mild-to-moderate AD and mild AD (Alzforum 2017, Alzforum 2017c, Lilly 2016, Merck 2017, Mo 2017, Stat News 2017). However, there have also been recent encouraging or neutral interim results from Phase 1 and 2 studies in prodromal/mild AD, as well as changes to the development programs for some of these drugs to improve the probability of success in later trials. For example, changes include a focus on populations earlier in the AD continuum, especially prodromal AD and preclinical AD.
Additionally, an increase in the dose has been implemented for several Aβ antibodies in development (Alzforum 2017c).

While the negative results were disappointing, they also clarify that additional data are necessary to determine the relationship between biomarkers and clinical outcomes and to optimize dose and target population (or stage of disease). Currently ongoing studies of these and other compounds include many of the same biomarkers and clinical outcomes, which should provide additional data and allow greater refinement in directing research.

**Shift in research emphasis: earlier in the disease progression**

Over the past two years, there has been a marked shift in AD research, as both industry and academic researchers have increasingly focused earlier in the disease progression, notably preclinical AD research and drug development, including secondary prevention trials (Reiman 2017). Dubois (Dubois 2017) describes this “conceptual shift” as a focus on treatment as early as possible in the disease progression, a wise course given that biomarkers can detect the disease pathology ten to twenty years before symptoms emerge. Similarly, the important work of the Dementia Discovery Fund drives diversification of the modes of action that are being explored across the spectrum of disease and aggregation of the data necessary to understand the root causes of the disease and its progression.

This new focus on preclinical AD brings specific challenges in developing drugs for AD primary prevention (in individuals who are amyloid-negative) or secondary prevention (in individuals who are amyloid-positive, (preclinical AD)). First and foremost, given that individuals are presymptomatic and most clinical outcome assessments (COAs) used for AD dementia trials are insensitive to detecting changes in this early population (Ritchie, 2017), it is critical to identify the appropriate patients and outcome measures to be included in primary and secondary prevention drug trials. Typically, this is one of the most costly and lengthy aspects of Phase 3 development. In secondary prevention studies, after identification of the appropriate participants, treatment duration needs to be four to five years, and even longer treatment is necessary for primary prevention (McDade 2017).

It is also important to identify risk factors with strong predictive properties of the future course of the disease to ensure that appropriate candidates are enrolled in these long-duration studies. Reiman and McDade identify some challenges to both primary and secondary prevention studies, including the need to attract large numbers of healthy candidates for trials, the need for sensitive cognitive outcomes, the very limited number of people with dominantly inherited Alzheimer’s disease, and the high cost of prevention studies. However, the benefits for society and for governments from successful prevention studies would be immense.

Clinical outcome measures also present challenges, especially in the earlier stages of AD. Cognitive decline precedes, and predicts, functional decline in the natural course of the disease (Zahodne 2013, Liu Seifert 2015b). Early in the disease it is more difficult to detect functional impairment or treatment effects on function in populations using currently-available tools (Siemers 2016). As a result, studies evaluating the efficacy of interventions in these earlier populations utilize cognitive endpoints. For similar reasons, in early AD stages regulators
should consider cognitive benefits – DMTs slowing the rate of decline, or symptomatic treatments showing improvement from baseline – as the markers of treatment efficacy for acceptance.

**Biomarkers: diagnostic evolution and the search for surrogates**

Along with the broader research effort, there has also been recent collaborative work across academia, industry, and regulators to revise research criteria for diagnosis of AD. This includes the “A-T-N” (amyloid, tau, neurodegeneration) biomarker classification, along with clinical findings. These criteria better recognize the core pathophysiology of AD and further solidify the increasingly accepted concept of AD as a disease continuum that begins many years before the onset of clinical symptoms (Jack 2016, Jack 2017, Arneric, 2017, Lewczuk, 2017, NIA-AA 2017). However, there are challenges to implementation of these diagnostic criteria, first in developing a research framework and eventually in clinical practice, including inconsistent availability of biomarker tests in different geographical regions, and lack of reimbursement of approved biomarker tests in some regions. Applying these ATN criteria will add costs for MRI, amyloid and tau testing, while capacity constraints will limit application of these biomarker-driven diagnostic criteria.

Additionally, in the context of drug development, biomarkers can be considered to be Drug Development Tools (DDTs). FDA, EMA, and PMDA have established DDT qualification pathways as a way to provide a framework to evaluate and adopt new tools into regulatory decision making in drug development, and, depending upon data available, to define the appropriate context-of-use for use in a drug development program. FDA also allows use of biomarkers in registration studies when alignment is reached with the sponsor for an individual drug development program.

The absence of surrogate biomarkers that are accepted by the AD research field or considered validated or qualified for specific contexts of use by regulators has proven to be one of the most challenging aspects of both AD research and drug development. As PMDA notes, it is “desirable to establish indicators that would enable detection of even slight changes in cognition, and biomarkers that would allow prediction of the clinical responses to treatment” (PMDA 2017). FDA and EMA have expressed similar views.

This challenge is particularly urgent for secondary and primary prevention studies; wide acceptance of a surrogate biomarker endpoint in these studies would help considerably to address the challenges of long-duration studies. Because an effect on a biomarker should be discernable prior to a clear separation on a clinical endpoint, biomarker-based approvals could bring treatments to patients more quickly, which would be particularly important in studies designed to prevent or delay onset of AD.

Considering the urgent need for new therapeutics in AD and the size and cost of clinical trials, use of accepted surrogate biomarkers will eventually be an important tool for both industry and regulators. We encourage regulators to consider what levels of evidence would be sufficient to permit biomarkers to be used for conditional approvals, or, eventually, for full or accelerated
approvals (e.g., for a primary prevention indication). There have been three key barriers to advancing the identification and acceptance of surrogate biomarkers for AD; the first of which has been the lack of positive Phase 3 studies of DMTs. However, as the research framework shifts to greater use of biomarkers, additional evidence will become available to assess potential correlation between biomarkers and clinical effect. Second, it has been challenging to address potential risk in sharing biomarker data across multiple industry stakeholders. The proposals presented at the 2017 Lausanne IV meeting regarding precompetitive biomarker data sharing from AD trials could help allow earlier identification and qualification of potential surrogate biomarkers for AD to further advance the field (Truyen 2017). Wider adoption of data sharing principles outlined by the Collaboration for Alzheimer’s Prevention (CAP) would be a key step forward (Weninger 2016) toward providing more comprehensive biomarker data to support development of biomarker DDTs. Finally, development of the infrastructure for a global, fully integrated, actionable CDISC standardized database where disease progression models and DDTs can be developed should be supported.

“Novel-novel” and combination treatments: an expanding area of research

In addition to amyloid and tau, the push to explore further other possible mechanisms of action in AD increases the likelihood that combination therapy will become an important area of research, clinical trials, and treatment. Similarly, the negative results with some single action therapies has encouraged researchers to investigate the potential benefit of attacking two different neurodegeneration mechanisms concurrently. While this raises some unique challenges for drug development (Hendrix et al. 2016), all stakeholders agree that combination therapy may become necessary for optimal treatment of AD at various stages.

As we wrote in 2016, factorial trial designs are often recommended for study of novel-novel combination treatments, as they permit study both of individual treatments and the interactions between treatments. As AD studies are already large, long, and costly, applying strict factorial design criteria makes studies of “novel-novel” combination therapies even more challenging and potentially cost-prohibitive, as the EU has recognized (EMA 2016). FDA has similarly expressed openness to consider other options in design of Phase 3 studies (FDA 2013b).

The shift to attention on intervention earlier in the AD continuum raises the hope that combination treatment (including combination of DMTs and new symptomatic/neurotransmitter agents and combinations of DMTs with other DMTs), may change the clinical course of the disease and its treatment, allowing AD to be treated similar to other chronic conditions – using combinations of medicines with different mechanisms of action to allow patients to maintain cognition and function for a longer portion of their lifetime.

Finally, as multifactorial diseases require a broader approach, and AD is no different, the field will need a broader approach to understand what will help spur development of combination therapies, including the growing interest in novel-novel combination therapies, and the challenges in designing and conducting these types of clinical trials.
RECOMMENDATIONS FOR ACTION

The fight against AD can only be advanced through collaborative efforts by all stakeholders. This includes regulators as well as other policymakers, academia, industry, and patient and advocacy groups. For the important role of regulators, we reaffirm the basic theme of our 2016 paper: that regulators continue to exercise flexibility in reviewing the work that sponsors offer as new compounds go through development. Beyond this, we suggest some specific points for regulators’ consideration:

- It is currently unknown which clinical scales will best detect treatment effects on the subtle cognitive deficits in early stages of AD. Therefore, similar to their approach to evaluating biomarker data, regulators could consider allowing a more holistic weight-of-evidence type of approach to determining clinical efficacy in early stages of AD. In addition, cognitive composite endpoints, which capture those components from existing scales that have the ability to discern decline in earlier AD populations, should continue to be used and should be considered for qualification.

- Given the Digital Health Initiative supported by FDA, and FDA’s requirement of CDISC standards for registration submission, FDA and other regulatory agencies should encourage the development of CDISC standards that would support the use of novel, and more sensitive digital technologies for acceptance as outcome measures (Arneric 2017; Dorsey 2017; Torous 2017; Neville 2017). Using these more sensitive continuous assessments could dramatically reduce the cost of clinical trials up to 80% (Dodge 2015).

- FDA now accepts a single primary endpoint for approval of treatments for prodromal AD and for accelerated approval for preclinical AD. Clinical trial results, particularly treatment effects on cognition, should inform how regulators view measures of outcomes in later, dementia stages of the disease (Researchers Against Alzheimer’s 2017). Given the substantial overlap between prodromal AD and mild AD and the fact that these populations are often included together in clinical trials, it would be appropriate to include mild AD as part of the final guidance for early AD trials and consider accepting similar primary endpoint options.

- Sponsors have considered alternatives to traditional trials to increase efficiency in AD drug development in Phase 1, 2, and 3, and regulators have shown flexibility and openness to innovative designs. In AD, specific challenges exist because of the absence of accepted surrogate biomarkers, but both FDA and EMA have been open to considering adaptive design in drug development (FDA 2010, EMA 2007) and to delayed-start trial design as supportive for disease modification (EMA 2016, FDA 2013). It would be helpful to develop a consensus across academic, industry and regulatory stakeholders on statistical methods for delayed-start trials in AD. Statisticians across industry and academia have expressed interest in collaborating and forming a pre-competitive, cross-functional research working group to address 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.

- Regulators should continue to encourage public-private partnerships to help support the very long duration of primary prevention trials and promote dialogue regarding innovative ways to protect patents and other intellectual property in primary prevention.
trials to incentivize investment in drug development despite the long development cycle these studies require.

- We hope regulators will be willing to engage in discussion of the potential to accept efficacy data from studies in familial AD (which can be conducted with smaller sample size due to less variability) to support approval for treatments for sporadic preclinical AD, which could result in shorter development timelines and earlier availability of treatments to patients,

- We urge regulators to continue to allow data from the AD research field to drive regulatory policy regarding eventual acceptance of surrogate biomarker(s) for approval of treatments for primary prevention, as in other therapeutic areas such as prevention of heart attacks (cholesterol lowering treatments) or AIDS (treatments that reduce viral load). Because more research is needed to support use of surrogate biomarkers in AD, this is a longer-term goal, and precompetitive biomarker data sharing should be encouraged.

- Increased dialogue between regulators and industry to develop labeling recommendations will guide health care professionals in identifying patients appropriate for treatment with drugs developed using the newly proposed diagnostic criteria. Regulators could consider whether to allow treatment of patients diagnosed based on medical practice with tests available in that region, rather than requiring specific tests in labeling.

- Similarly, the patient context is critical in addressing AD. FDA has recognized this and is working to include the patient perspective in regulatory decision-making (FDA 2013, 2015); EMA takes a similar approach.

- The labels approved for DMTs should distinguish DMTs from symptomatic treatments, and should reflect their mechanisms and treatment outcomes, so that prescribers and caregivers clearly understand the effects of these treatments and the phases of AD where they are effective.

The role of regulators is of course indispensable. Disappointing clinical results in some trials only heighten the importance of offering clarity and continued collaboration with other stakeholders. These trials, like others, are valuable as sources of data to inform future scientific investigations. With an eye towards the 2025 goal, regulators have worked to adopt innovative programs and to continue to refine guidance for researchers seeking to advance the field and bring new compounds to clinical development.

As with any multifactor disease, particularly one in which the research environment is changing so rapidly, flexibility is a very important aspect of regulatory policy. The flexibility that regulators have shown in this evolving field of AD has clearly encouraged research. Increasing harmonization among regulatory agencies, where possible, is welcome, and greater public discussion of new scientific developments would help industry to understand better the perspectives of different regulators. Additional data from clinical trials will continue to inform the entire community of AD stakeholders and provide a solid foundation for further research towards the development of effective treatments by 2025.
REFERENCES


