WHITE PAPER
IMS DISEASE INSIGHTS

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Innovative therapies for Alzheimer's disease

New treatments will drive significant market value growth over the next ten years

AUTHOR: PETER ALFINITO, PH.D., LEAD ANALYST, CNS DISORDERS, IMS HEALTH SYNDICATED ANALYTICS

Introduction

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder that initially impacts a patient's memory but ultimately leads to the loss of their ability to care for themselves. Current gold standard treatments for AD such as Eisai/Pfizer's Aricept (donepezil) and Forest's Namenda (memantine; also marketed by Lundbeck, Merz and Daiichi Sankyo as Ebixa, Axura and Memary, respectively) offer some symptomatic efficacy in early stages of the disease but, in later stages, these therapies become largely ineffective. In the absence of good treatment options, the healthcare costs associated with AD and other dementias are high and are expected to continue to rise substantially in the future. For example, in the US alone, AD healthcare costs are projected to increase from $200 billion in 2013 to $1.2 trillion by 2050. Thus, the lack of good treatment options for AD creates a heavy personal, societal and financial burden. In response to these challenges, researchers have undergone an intense search for new and more effective treatments.

While this effort has led to many different small molecule and biopharmaceutical approaches, the most promising of these are the disease-modifying agents which focus on reducing CNS levels of β-amyloid and its related aggregated structures. It is these innovative therapies that will provide significantly improved efficacy over existing treatments, revolutionize AD treatment paradigms and drive massive growth of the AD market. In our coverage of the nine major pharmaceutical markets (i.e. US, UK, France, Germany, Italy, Spain, Japan, China, Brazil) we forecast that the AD market will grow from $5.7 billion in 2012 to $19 billion by 2022, making it one of the fastest growing disease areas in the industry. This growth will be led by Eli Lilly's Solanezumab, the first β-amyloid-directed therapy to reach the market, but will ultimately be dominated by much easier to administer and potentially more effective small molecule BACE1 inhibitors. It is anticipated that development of disease-modifying treatments such as these will reduce the burden of AD on patients and caregivers as well as on healthcare systems across the globe.

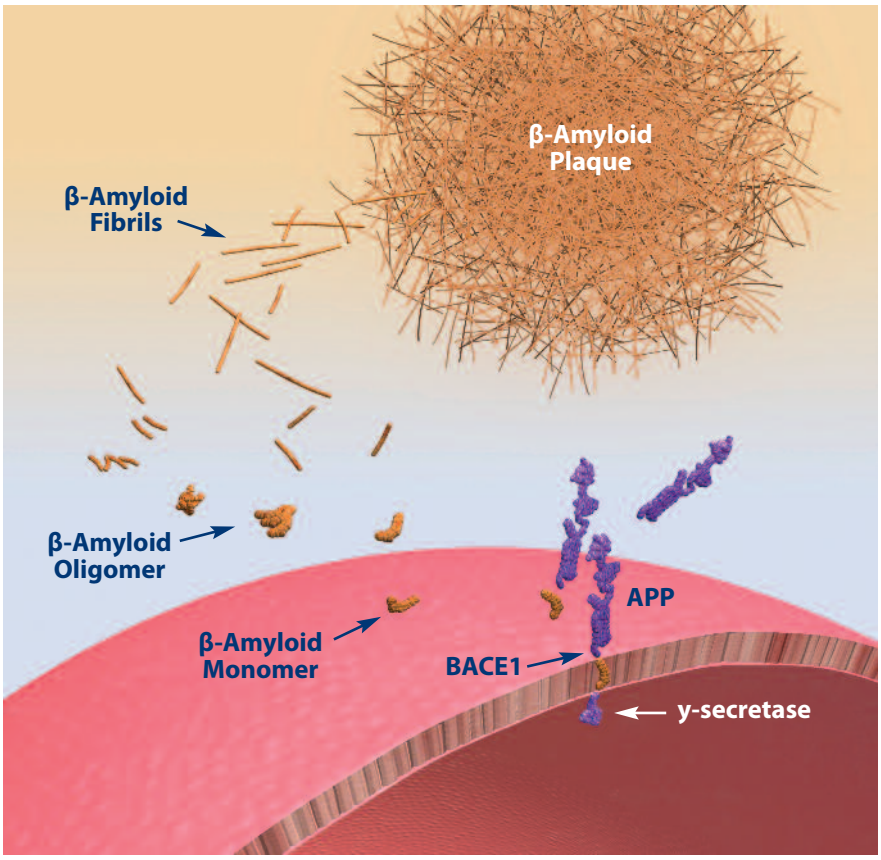
Amyloid-beta: a key target for the future AD market

While the exact cause of AD is still unknown, human genetic data combined with advances in preclinical animal models have provided researchers with several plausible hypotheses that revolve primarily around the well-described pathological hallmarks of the disease. The most prominent amongst these is the β-amyloid hypothesis (Figure 1) which has only recently been tested in large clinical studies through agents such as Elan/Pfizer's AN1792, Pfizer's/Johnson & Johnson's Bapineuzumab and Eli Lilly's Solanezumab. Although these attempts were not entirely successful, they have provided valuable insight into the potential pitfalls of drug development around β-amyloid and have been useful in refining the hypothesis as well as guiding development of the next generation of therapies.

Of the nine major pharmaceutical markets (i.e. US, UK, France, Germany, Italy, Spain, Japan, China, Brazil) we forecast that the AD market will grow from $5.7 billion in 2012 to $19 billion by 2022, making it one of the fastest growing disease areas in the industry.

β-amyloid is a major constituent of the extracellular, senile plaques which have defined the disease pathologically for over 100 years and is found primarily as fragments of the amyloid precursor protein (APP). These amyloid fragments are generated through the sequential processing of APP by the enzymes β-amyloid converting enzyme 1 (BACE1) and γ-secretase. Although released as individual monomers, the propensity for β-amyloid fragments to self-aggregate creates high-ordered protein structures in the form of oligomers, protofibrils and plaques (Figure 1). It is these aggregated forms of β-amyloid that have drawn the attention of drug developers as their aberrant accumulation in the central nervous system (CNS) appears to be an initiating factor in the dysfunction and ultimate death of the neurons that lead to AD.

FIGURE 1: THE B-AMYLOID HYPOTHESIS



Source: IMS Disease Insights, Alzheimer's Disease, IMS HEALTH, 2013

Consequently, many of the drugs currently in clinical development focus on reducing β-amyloid accumulation in the CNS as a means to delay or prevent neuronal cell death and ultimately modify disease progression.

Key β-amyloid-directed therapies currently in development include passive immunotherapies aimed at various β-amyloid species as well as small molecule BACE1 inhibitors (Table 1). While there are still several potential pitfalls in the β-amyloid hypothesis such as which form(s) of β-amyloid are the most toxic to neurons, who are the best patients to treat and when should treatment be initiated, it is grounded in good science and strongly supported by human genetic studies. Thus, many interviewed KOLs think β-amyloid-directed therapies have a high probability of success and the potential to dramatically alter AD treatment paradigms. IMS Health anticipates that these therapies will have a significant impact on the total value of the AD market over the next ten years.

Amyloid precursor protein is cleaved sequentially by BACE1 and γ-secretase to yield β-amyloid monomers. β-amyloid self-aggregates to form oligomers, fibrils and plaques. It is currently thought that these high-ordered structures of β-amyloid cause synaptic dysfunction and ultimately lead to neuronal cell death. Agents currently in clinical development aim to either block APP processing by BACE1 or bind various forms of β-amyloid through passive immunotherapies to reduce its CNS accumulation.

TABLE 1: KEY B-AMYLOID-DIRECTED THERAPIES IN CLINICAL DEVELOPMENT

Class	Drug (Co.)	Mechanism of action
BACE1 inhibitors	MK8931 (Merck & Co.)	Inhibits cleavage of APP precluding the production of β-amyloid
Passive immunotherapies	Solanezumab (Eli Lily & Co.)	Binds soluble β-amyloid in blood and draws β-amyloid from the CNS
	Gantenerumab (Roche)	Binds oligomers, fibrils and plaques to facilitate their clearance from the CNS
	Crenezumab (Roche)	Binds monomers, oligomers, fibrils and plaques to facilitate their clearance from the CNS
	BAN2401 (Eisai)	Binds fibrils to facilitate their clearance from the CNS

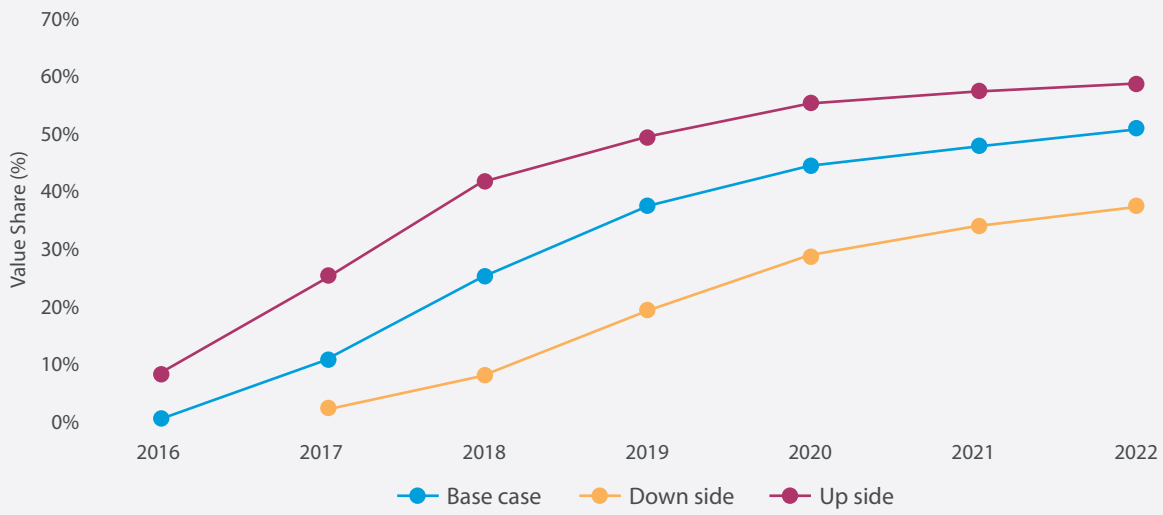
Source: IMS Disease Insights, Alzheimer's Disease, IMS HEALTH, 2013

Amyloid-beta-directed therapies will dominate the AD market

Despite many attempts to develop new pharmacological treatments for AD, there have been few successes in the recent past. Exceptions to this include lifecycle management activities such as extended release (Razadyne/Reminyl ER) and patch formulations (Exelon) of acetylcholinesterase inhibitors, which have offered greater convenience for some patients. However, these products have not changed treatment paradigms or the overall success of AD treatment. Difficulties in the clinic are not surprising as we lack an understanding of the exact cause(s) of AD, we have only a rudimentary understanding of the neurobiology of human cognition and lack reliable preclinical animal models. The predictable outcome of the lack of new products have been that the AD market has contracted over the last several years and that market growth over the next 2 years will be limited. For example, short-term growth will be primarily dependent on small increases in the treatable patient population due to aging of the general population, price increases for branded drugs such as Exelon TD, Namenda (US), Ebixa (France, Italy, Spain, China) and Memary (Japan) which are being challenged by governments and payers in every major market across the globe, and through lifecycle products such as Namenda XR and Arimenda which will have limited exposure in the worldwide market. Thus, none of these factors are expected to offer significant market growth and with patent protection for branded memantine expiring in most major markets by 2015, the worldwide AD market value will decline in the absence of new products. Despite past failures and limited growth over the next several years, the AD market will ultimately experience a revolution through the launch of disease-modifying, β-amyloid-directed therapies that will alter treatment paradigms and likely change the prognosis of AD. This scenario is similar to the revolution that occurred in the rheumatoid arthritis field where innovative and expensive disease-modifying therapies such as Pfizer's/Amgen's Enbrel altered treatment paradigms and restored growth to a highly genericized market.

IMS Health forecasts include three scenarios: Base case, Up side and Down side with the results of each scenario depending on the interplay of several variables in the market. Key β-amyloid-directed, disease-modifying drugs in the current forecast period (2012-2022) include the passive immunotherapies and BACE1 inhibitors (Table 1). Collectively, these therapies are expected to grow the AD market of nine major pharmaceutical markets (see above) 100% between 2012 and 2018 and by a total of 230% by 2022. This base case growth will be dependent on price premiums which are likely to be reimbursed by governments and payers due to a competitive advantage on efficacy, share steal from current symptomatic therapies based on improved efficacy, and increases in the number of treated patients based on optimism, by patients, physicians and caregivers, for a treatment with the potential to slow neuronal cell loss (i.e. disease progression) and not just treat the symptoms. The combined sales of Solanezumab, Gantenerumab, Crenezumab, BAN 2401 and MK 8931 are projected to capture 51% of the total AD market value of nine major pharmaceutical markets by 2022 (Figure 2). Uptake of these new therapies is expected to be slow at first as these agents cater to a less prevalent early AD population (Figure 2).

FIGURE 2: PROJECTED VALUE SHARE OF KEY B-AMYLOID-DIRECTED THERAPIES



Source: IMS Disease Insights, Alzheimer's Disease, IMS HEALTH, 2013

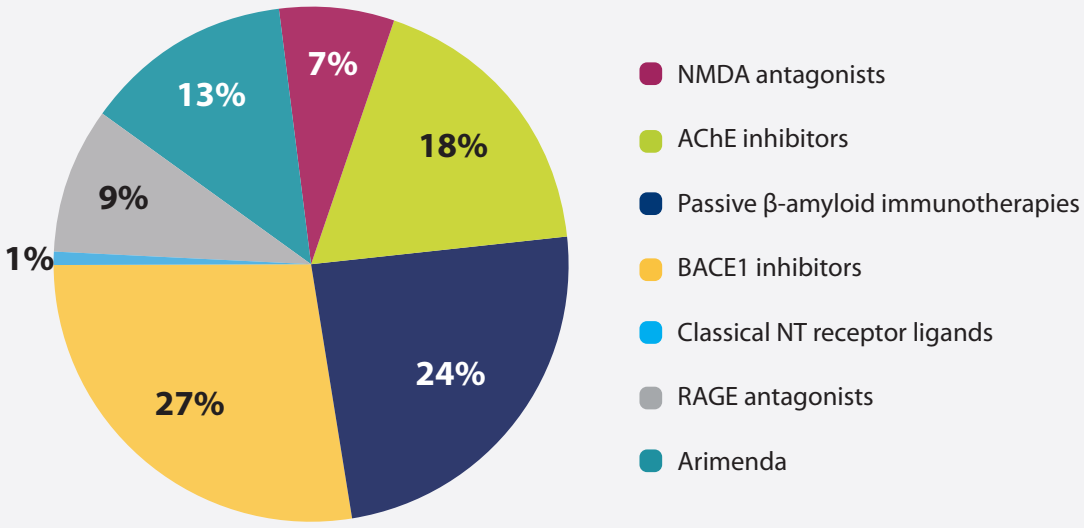
Projected Up side and Down side forecast scenarios showcase the potential maximum and minimum market share of these agents based on changes in the factors most likely to influence these therapies, such as price, launch date, share steal percentage and market uptake rate (Figure 2). In general, Up side scenarios assume higher price premiums, more rapid uptake, earlier launch dates (by 1 quarter) and higher share steal (by 15-25%) relative to the base case while Down side scenarios assume the converse. Overall, these projections provide a range of 1.5 billion dollars between Up side and Down side cases in the year 2022 and suggest the market could grow as much as 380% or as little as 125% between 2012 and 2022.

BACE1 inhibitors are the most promising AD drugs to be launched over the next ten years

Passive immunotherapies and BACE1 inhibitors address the β-amyloid hypothesis from two different mechanisms of action and, as a result, IMS Health projects the efficacy of these two classes and the value of each individual drug will differ accordingly. BACE1 inhibitors block β-amyloid production by inhibiting the enzyme responsible for APP cleavage while the passive immunotherapies attempt to clear aberrantly accumulated β-amyloid after it has been enzymatically processed from APP. Although seemingly small, this difference in the mechanisms of action changes both the probability of success and the potential market share for the drugs in these classes. These ideas are based on perhaps the most convincing human genetic support for the β-amyloid hypothesis that exists. In a recent study, a mutation located near the BACE1 cleavage site in APP was found to lower the risk of developing AD. This study strongly suggests that APP processing is a major contributor to the etiology of AD and also indicates that the relevance of the β-amyloid hypothesis extends beyond the familial, early-onset form of the disease to encompass the broader sporadic AD population. Thus, unlike the passive immunotherapies which exert their effects after APP has been processed, BACE1 inhibitors work in a similar fashion as the naturally occurring protective genetic mutation and limit APP processing.

IMS Health analysts and interviewed neurology experts agree that, based on the mechanism of action, BACE1 inhibitors hold the greatest promise of the disease-modifying treatments currently in development for AD. The most advanced BACE1 inhibitor is MK 8931 and no other compounds from this class are anticipated to launch in the next ten years. Thus, IMS Health projects that, once launched, Merck's MK 8931 will capture the highest market share (27% by 2022) of any individual drug on the AD market (Figure 3). In comparison, the entire passive immunotherapy class is expected to have a similar market share to MK 8931 by 2022.

FIGURE 3: DISTRIBUTION OF FORECASTED VALUE SHARE FOR ANTI-ALZHEIMER'S DRUG CLASSES IN 2022



Source: IMS Disease Insights, Alzheimer's Disease, IMS HEALTH, 2013

Solanezumab will be the first disease-modifyng treatment on the AD market

The β-amyloid hypothesis is still in its infancy and questions remain around which β-amyloid species is the best target, which patient population will respond best and at which stage of the disease to initiate treatment. Nonetheless, our current understanding of the science behind the β-amyloid hypothesis suggests this mechanism is a key component of the etiology of AD. Although there have been several β-amyloid-directed therapies that have failed in the past, pharmaceutical companies have incorporated their learnings around side effects, patient populations and recruitment criteria into more refined clinical trial strategies and, as a result, there is optimism around the future potential of this class of drugs.

The most advanced β-amyloid-directed therapy is Solanezumab. Although Solanezumab failed to meet its primary efficacy endpoints through EXPEDITION 1 and 2, secondary analysis indicated there was an effect in mild AD patients. This analysis provided the support needed to conduct an additional phase III study called EXPEDITION 3 in a refined patient population that includes only mild AD patients with clear amyloid positive PET scans. These changes are expected to increase the probability of success for Solanezumab as the first disease-modifying AD treatment to reach the market. Results from this study are eagerly anticipated in the next several years across academic, government, social and pharmaceutical sectors as the outcome is not only tied to Eli Lilly's success but to the success of the β-amyloid hypothesis itself, the multitude of other companies targeting this pathway and the patients, caregivers and physicians who are desperate for a more effective treatment for AD.

About the author: Peter Alfinito, Ph.D. is a neuroscientist with over 18 years of academic research and pharmaceutical drug discovery experience in the areas of Alzheimer's and Parkinson's diseases, depression, schizophrenia, migraine, women's health, retinal degeneration and infectious disease. Dr. Alfinito's prior pharmaceutical experience includes roles at Wyeth, Bristol-Myers Squibb and Merck where he led target validation, lead optimization and clinical biomarker teams in drug discovery and phase I clinical trials. Dr. Alfinito has 19 publications in peer-reviewed journals including first-author publications in the Journal of Neuroscience and Proceedings of the National Academy of Sciences. Dr. Alfinito earned a B.A. in chemistry from Swarthmore College and a Ph.D. in Neuroscience from the University of Medicine and Dentistry of New Jersey, where he was awarded the prestigious Stanley S. Bergen Medal of Excellence. Dr. Alfinito is currently the CNS Lead Analyst at IMS Health where he is drawing on his rich research and industry experience to provide market analysis and pipeline insights on CNS diseases.

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IMS Health

EUROPE & WORLDWIDE
210 Pentonville Road
London N1 9JY
United Kingdom
Tel: +44 (0)20 3075 5888

THE AMERICAS
One IMS Drive
Plymouth Meeting
PA 19462
USA
Tel: +1 610 834-0800

ASIA-PACIFIC
8 Cross Street #21-01/02/03
PWC Building
Singapore 048424
Tel: 65-6227-3006

JAPAN
Toranomon Towers Office 4-1-28
Toranomon, Minato-ku
Tokyo 105-0001
Japan
Tel: 81-3-5425-9000

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