Expert therapy area review of the key market players and deals highlights for leading areas of industry investment and development. These insightful reviews are based on the strategic data and insights from Thomson Reuters Cortellis™ for Competitive Intelligence.
ABSTRACT

Alzheimer's disease is a condition without a cure; it affects 35 million people worldwide and care costs in the US alone are on course to reach $1.1 trillion by 2050. To date, no drug has reached the market that is able to even slow its progress – currently approved agents treat only its symptoms, and not even those for very long. Despite the desperate need for a breakthrough, the area has been a marginalized one, with funding in very short supply. Expectations have been further dampened by the recent failures of several late-stage and previously promising agents. However, a number of recent advances have cast a more hopeful light on this potentially lucrative field. The US Government has pledged $130 million for R&D into the disease, with a further $26 million for ancillary issues such as carer support. New diagnostic agents are entering the market that will help identify and treat patients, and a number of studies investigating the very early stages of the disease have been launched.
Alzheimer’s Disease International, the worldwide federation of Alzheimer’s disease (AD) associations, has estimated that AD, the most common form of dementia, affects more than 35 million people worldwide, with patient numbers expected to nearly double every 20 years. In the US it is the sixth-leading cause of death, with care costs predicted to be $200 billion in 2012, rising to $1.1 trillion by 2050. However, this huge market opportunity remains poorly served. Between 2000 and 2008, when mortality from breast cancer, prostate cancer, heart disease, stroke, and HIV declined by 3 percentage points to 29 percent, AD mortality increased by 66 percent. Furthermore, AD is the only one of the top-ten leading causes of death in the US that cannot currently be treated, prevented, or slowed.

Currently available treatment options for AD provide temporary symptomatic relief - acetylcholinesterase (AChE) inhibitors such as Aricept, Exelon, and Razadyne increase acetylcholine levels to preserve neuronal communication in the short term, while NMDA antagonists such as Namenda block low-level pathological activation of NMDA receptors to temporarily improve neuronal function. However, neither halts the neuronal death that underlies disease progression. Nevertheless, even without a cure or preventative agent, the AD market is a lucrative one. Aricept alone generated $3.316 billion in revenue at the market’s peak in 2010, with Aricept, Exelon, Razadyne, and Namenda generating combined sales of $6.443 billion that year. However, according to Consensus data from Thomson Reuters Cortellis™ for Competitive Intelligence, combined sales of these four drugs are set to fall to $3.558 billion by 2016 (see Figure 1), by which time all four will be facing generic competition, as well as potential competition from drugs currently in development.

**FIGURE 1: SALES FIGURES (2000 TO 2011) AND CONSENSUS FORECAST SALES (2012 TO 2016) FOR ARICEPT, EXELON, RAZADYNE AND NAMENDA**
The lack of a cure for AD means that this pharmaceutical area is a diverse one, with new treatment approaches being explored. The most advanced of these involves the inhibition of the amyloid beta (Abeta) protein, which has been postulated as a causative agent of AD. However, recent failures in this area, for example the discontinuation of the phase III Abeta-targeting drug bapineuzumab, have cast doubt on this hypothesis, although it is also possible that targeting Abeta could work if only treatment were begun at an earlier stage in the progression of the disease. Several new studies are taking this into account, although utilization of this theory is hampered by the difficulty of identifying potential AD victims before the cognitive changes become manifest. Less than 5 percent of AD cases are genetically inherited, leading to an early-onset form of the disease, with the rest occurring at random in subjects usually aged over 65.

The recent entry into the market of Abeta-imaging agents as diagnostic tools will also help the development of these therapeutic agents. AD research has also been limited by the long-term issue of lack of funding in the area. In 2011 the Alzheimer’s Association noted that the NIH spent only $480 million on AD research, compared with $6 billion for cancer, $4 billion for heart disease and $3 billion for HIV/AIDS. However, this is beginning to change, with large government funding initiatives recently announced in the US.

This increase in funding, combined with the recent approval of the AD diagnostic imaging agent Amyvid, is likely to reinvigorate the field. With improved diagnosis and brain imaging will come better understanding of the disease process, plus the ability to recognise, and therefore treat, the disease at an earlier stage. New ideas as to the causes of Alzheimer’s disease pathology are also being postulated, such as a link to insulin levels, potentially opening the way for new treatment methods. A number of drugs in development will be discussed in this report, with the primary focus being on drugs in late-stage clinical development.

“For millions of Americans, the heartbreak of watching a loved one struggle with Alzheimer’s disease is a pain they know all too well. Alzheimer’s disease burdens an increasing number of our Nation’s elders and their families, and it is essential that we confront the challenge it poses to our public health.”

Barack Obama, US President
CURRENT TREATMENTS

Although the four main drugs currently on the market for AD cannot alter the underlying disease pathology, Aricept, Exelon, Razadyne, and Namenda can offer temporary relief from the cognitive manifestations of the disease via addressing neurotransmitter defects in the brains of AD patients. AChE inhibitors help to preserve memory function, and can delay the worsening of symptoms, in about half of the patients that take them, by about 6 to 12 months. NMDA antagonists can also temporarily delay the worsening of symptoms in some people and can be used in conjunction with drugs of the AChE inhibitor class.

ARICEPT

Eisai’s Aricept, the first specifically designed AChE inhibitor to reach the market (in 1997), is also the only one of the three AChE inhibitors that is indicated for all stages of AD, from mild cases to severe; Exelon and Razadyne are indicated only for mild to moderate disease. The drug has a convenient, once-daily dosing schedule and is available in a range of formulations, including tablets, rapid disintegration tablets, an oral jelly, and a higher-dose sustained-release formulation. However, Aricept’s clinical effect is only marginal: in a 15-week trial it showed a difference of 2.7 to 3.0 points on the AD Assessment Scale-cognitive subscale (ADAS-cog) compared with placebo, but clinical decline after three years was no different to placebo in a 769-patient study. Aricept generics entered the market in 2010, causing a swift decline in sales from $3.454 billion in 2009, down to $1.854 billion in 2011; by 2015, it is anticipated that the drug will have lost its blockbuster status, with Cortellis for Competitive Intelligence listing Consensus sales of $962.6 million.

EXELON

Sales of Exelon, which was launched on the US market by Novartis three years after Aricept, were initially limited by its twice-daily dosing regime and significant gastrointestinal side effects. The introduction in 2007 of a daily transdermal patch formulation, which increased dosing convenience and reduced the side effects, boosted Exelon sales, but its highest sales recorded to date - $1.067 billion in 2011 - remain less than a third of Aricept at its peak. However, in the phase IV CENA713IA09 study Exelon was shown to provide significant clinical benefit over Aricept in patients with concomitant Lewy body disease or who fully express the butrylcholinesterase enzyme. Of the three AChE inhibitors for AD, Exelon is also the only one also approved for mild-to-moderate dementia associated with Parkinson’s disease. Like Aricept, Exelon has faced generic competition since 2010.
RAZADYNE

Johnson & Johnson (J&J), Shire, and Takeda’s Razadyne was the third AChE inhibitor to enter the AD market, but the first to face generic competition (from 2008). It has the smallest market share, with 6.65 percent of sales at the $6.443 billion market peak in 2010. Even following generic erosion of Aricept sales in 2011, Razadyne’s share only rose to 10 percent of the then $5.511 billion market. The drug’s third-in-class status and early generic challenge is likely to play a part in this, although there is also evidence that Razadyne is less clinically effective than the other two treatments. Meta-analyses published in 2008 and 2009 showed that patients treated with Razadyne have less chance of a global response, less adherence to treatment and more gastrointestinal side effects compared with Aricept. A prospective trial in 938 subjects published in 2010 showed a significant worsening of neuropsychiatric inventory and instrumental activities of daily living scores with Razadyne compared with Aricept at week 36 of treatment.

NAMENDA

Namenda was the first drug available for moderate-to-severe AD, following its launch onto the AD market in Europe in 2002 by H Lundbeck and onto the US market by Forest in 2004; Aricept’s use was extended from mild-to-moderate disease to include severe disease in 2006. Namenda is also the first and only NMDA receptor antagonist on the market, a fact that is reflected in its continued blockbuster status. Cortellis for Competitive Intelligence expects peak sales of $2.575 billion in 2013, but Namenda is not anticipated to drop below the billion dollar sales mark until 2017. A strength of the drug is that it can be used in combination with AChE inhibitors; Namenda plus Aricept improved cognitive function in the phase III MEM-MD-02 trial compared with the decline in function seen with Aricept alone. AD Cooperative Study inventory-Activities of Daily Living (ADCS-ADL) scores declined less with the combination regime than with just Aricept therapy. In addition to this, Namenda is a valuable option for patients who do not tolerate AChE inhibitors, due to its low rate of gastrointestinal side effects. However, these advantages must be weighed against the inconvenience of Namenda’s twice-daily dosing regime, and its failure to gain approval for mild AD. Like the AChE inhibitors, Namenda’s efficacy is only modest and does not halt or slow disease progression. Compared with this, the newer drugs approaching the market behind the AChE and NMDA blockers have been hoped to be able to stop the disease in its tracks.
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FIGURE 2: MECHANISMS OF ACTION FOR A SELECTION OF THE ALZHEIMER’S DISEASE-TARGETING AGENTS IN LATE-STAGE DEVELOPMENT
A large number of the drugs in the AD pipeline target the Abeta protein (see Figure 2), in the hope that this could be the key to halting the effects of AD on the brain. Abeta is the main component of the deposits, termed amyloid plaques, found in the brains of AD patients, and it is hypothesized that Abeta plays a significant causative role in the disease. Several methods to attack the Abeta protein have been tried, although to date there has been little success: the AD field is littered with Abeta-targeting agents that fell by the wayside due to lack of efficacy or side effects.

**AN-1792**

Elan and Wyeth’s Abeta mimic, AN-1792, was designed to work as an immunization against the build up of Abeta deposits. It showed positive results in a phase IIa trial, improving memory, slowing the progress of AD-related disability and reducing Abeta plaques. However, in the same trial the drug also caused encephalitis in about 6 percent of patients, and so in 2002 its development was halted.

**FLURIZAN, SEMAGACESTAT AND AVAGACESTAT**

Modulation of gamma secretase to reduce Abeta levels was another approach tried. Flurizan, under development by Myriad Genetics and Encore Pharmaceuticals, showed trends towards slowing the decline of cognition in a phase II trial, although it missed the study’s primary endpoint. In 2008, the drug was discontinued after showing no significant effects on cognition or daily living but signs of increased side effects in a phase III trial. Clinical data for Eli Lilly’s gamma secretase inhibitor, semagacestat, were even worse. In August 2010 it was revealed that in the phase III IDENTITY and IDENTITY 2 studies, compared with placebo the drug worsened cognition and the ability to perform daily-living activities and increased the risk of developing skin cancer. It too was dropped. Worse still, the negative effect of the drug was not reversible – at seven months after treatment was stopped, the semagacestat patients still had poorer cognition and function that the placebo recipients, although at least the accelerated rate of decline in the semagacestat group had stopped. These data raise concerns for the ongoing development of Bristol-Myers Squibb (BMS)’s gamma secretase inhibitor, avagacestat. Phase II data presented in July 2011 showed potential for negative effects on cognition at higher doses, and the possibility of a skin cancer risk too. As of June 2012, the drug was still listed on BMS’s pipeline, although the phase III trials initially planned for 2010 have yet to begin.

**DIMEBON**

Another drug that showed initial promise, but then went on to disappoint, was Medivation and Pfizer’s Dimebon. The mechanism of action for the drug is unknown, although it is believed to improve mitochondrial function in the setting of cellular stress and to inhibit the toxic effects of Abeta. In the Russian phase II DIM02 study, the drug improved memory and thinking, activities of daily living, behavior and overall function at six and 12 months.
compared with placebo. At 18 months, the drug was shown to have preserved function across all key aspects of AD at or near the levels exhibited at enrollment. However, Dimebon failed to improve cognition, global function, daily living activities or behavior in the phase III CONNECTION trial, or cognition and daily living activities in the phase III CONCERT study. In January 2012, development of the drug was discontinued.

**GAMMAGARD**

Baxter International’s Gammagard is another potential AD therapeutic agent with a mechanism of action putatively tied to Abeta inhibition. The drug comprises highly purified immunoglobulin G derived from human plasma, and is already on the market for treating immunodeficiency disorders. Preclinically the drug has been shown to bind Abeta, and phase II data are very promising. In early 2008, the phase II trial met its primary endpoint of improving ADAS-Cog and global function scores compared with placebo at six months. Even more significantly, after a further 30 months’ open-label treatment, favourable outcomes with regard to thinking abilities, behavior and daily function were seen in the 11 patients who received Gammagard for the full 36 months. Of these patients, the four who were dosed with 0.4 g/kg of Gammagard every two weeks showed no decline on several standard cognition, memory, daily function and mood measures. These data represents the first report of long-term AD symptom stabilization, and as such, Gammagard, almost alone among Abeta-targeting agents, remains a hopeful prospect for AD treatment. Phase III development is underway, with data from the phase III, 390-patient, GAP study expected in the first half of 2013. A second phase III trial is to complete by 2015.

**PONEZUMAB**

Targeting Abeta using monoclonal antibodies (mAbs) has also been assessed as a potential therapy for AD, but this method has so far met with as little success as many previous approaches to Abeta inhibition. Pfizer’s ponezumab was investigated in a couple of phase II trials, but failed to have any effect on cognitive and functional outcomes; further development was not pursued.

**BAPINEUZUMAB AND SOLANEZUMAB**

Elan, J&J and Pfizer’s bapineuzumab progressed further than ponezumab but ultimately met the same fate. Despite failing its phase II endpoint, four phase III trials, plus three extension studies, were initiated from 2007 to 2009. In early August 2012, the first two of the phase III trials failed to meet their cognition and functional performance endpoints, and all ongoing trials of the drug were stopped. Although the likelihood of success in the trials had been estimated to be very low, with a stratified medicine model developed by the Massachusetts Institute of Technology predicting only a 26 - 36 percent chance of a positive outcome, the results were none-the-less disappointing. Taken in conjunction with previous Abeta-blocker failures, they raise the question of whether Abeta is the right target for AD treatment.

“The future of the beta amyloid approach to treatment of Alzheimer’s disease now lies in the balance.”

Deutsche Bank
When bapineuzumab failed, all eyes turned to Eli Lilly’s anti-Abeta mAb, solanezumab, as the next, and possibly the last, hope for the Abeta hypothesis. Expectations were not high, and to a degree this was borne out in late August 2012 by the failure of the drug to meet the primary cognitive and functional endpoints in two phase III trials, EXPEDITION 1 and EXPEDITION 2, in patients with mild to moderate AD. However, it did show a significant 34 percent reduction in cognitive decline in those patients with mild disease, making it the first anti-Abeta agent to do so in phase III trials. Whether this is due to solanezumab’s preferential binding to the soluble form of Abeta, compared with bapineuzumab’s preference for the fibrillar/plaque form of the protein, is not yet known. At the moment, development of solanezumab is continuing, although its chances of approval appear small.

An analysis of the bapineuzumab data was published the month following the solanezumab data announcement. One possible reason put forward for bapineuzumab’s failure was that a greater reduction in Abeta levels may have been needed in order to see a clinical effect. A second possibility was that therapy with bapineuzumab might need to be started much earlier in AD progression, possibly even before symptoms appear, in order to be effective. Separately, this same possibility has also been suggested in connection with Dimebon’s failure, and may also explain solanezumab’s effect in patients with milder, and therefore earlier-stage, disease. It is conceivable that by the time current Abeta-targeting treatment begins, irreversible brain damage cascades have already begun, such that even reducing the Abeta plaques, such as achieved by AN-1792, cannot halt AD progression.

**EARLY ALZHEIMER’S TREATMENT**

The possibility that AD drugs are being tested too late in the progression of the disease is of great relevance not only to the drugs to whose failure it may have contributed, but also to the Abeta-targeting drugs that are following behind those agents, such as Roche’s human anti-Abeta mAb gantenerumab.

Gantenerumab is being assessed in early-stage AD. The phase II SCarlet RoAD trial began, in January 2011, to enroll patients aged over 50 with prodromal AD, i.e. those who were not on any AD medication but who had recently begun to show signs of memory deterioration. In June this year, Roche converted the trial to phase III and raised enrollment from 360 patients to 770, potentially making the study a pivotal one from which the data could be used to secure marketing approval of the drug. Data are expected in 2015. Phase I data have shown that gantenerumab dose-dependently reduced brain Abeta levels, although two cases of vasogenic edema, an accumulation of extracellular fluid in the brain, were also seen.

—we believe the pooled data support the amyloid hypothesis, as these are the first phase III data with an anti-beta amyloid agent that appear to show a slowing of cognitive decline.”

Jan Lundberg, PhD.
Executive Vice President of Science & Technology, Eli Lilly & Co; President, Eli Lilly Research Laboratories
ALZHEIMER'S PREVENTION

In the Antioquia region of Colombia, AD affects not just a few people in old age, but thousands, with an average age of onset of just 45. This is the early-onset inherited form of the disease; these people are part of an extended family, descended from just one couple, who carry a mutation in the presenilin 1 gene that causes impaired cellular protein recycling, resulting in nerve cell death and early onset of AD. The Glu280Ala mutation is a dominant one, meaning that all carriers of it will go on to develop AD. By identifying carriers before the onset of disease, researchers can investigate whether a given treatment can prevent AD from developing. This extended family has provided the opportunity for the first ever AD prevention trials.

The humanized anti-Abeta mAb crenezumab is being developed by AC Immune and Roche's subsidiary Genentech. Crenezumab as yet has no clinical data beyond phase I, but it is a crucial drug to watch because it is the first anti-Abeta agent chosen for assessment of its ability to prevent AD, in the first of three upcoming trials for AD prevention in asymptomatic subjects.

The Banner Alzheimer's Institute, University of Antioquia and the National Institutes of Health (NIH) announced in May 2012 the initiation of the Alzheimer's Prevention Initiative (API), and its cornerstone trial that will assess the ability of crenezumab to prevent AD onset in the Colombian extended family. Crenezumab was chosen from 25 contenders largely because it does not induce vasogenic edema, which has been seen with drugs similar to crenezumab, such as bapineuzumab and solanezumab which at that time were still in active development. Fewer side effects may mean higher doses can be used, potentially increasing the drug's efficacy.

The API trial will enroll 300 subjects from Colombia, as well as up to 24 US subjects who are at high risk of developing AD because their family history indicates similar early-onset-AD-implicated mutations. They will be asymptomatic, aged over 30 years, and within 15 years of the age at which their parents developed AD. Change in cognition score is the primary endpoint of the five-year study, which is anticipated to start in 2013. An interim analysis will be conducted at 24 months.

Elderly subjects with raised Abeta levels are the targets of the second AD prevention trial in asymptomatic people. The anti-amyloid treatment in asymptomatic AD (A4) trial has been proposed by the ADCS and is to start in 2013. It will assess the effect of one drug, as yet not chosen, on cognition and function in patients aged over 70. The drug is likely to be an Abeta-targeting mAb.

The third AD prevention trial will be conducted as part of the Dominantly Inherited Alzheimer Network (DIAN) study that aims primarily to collect information on the biochemical brain changes that precede the start of AD symptoms. As part of DIAN, a Therapeutic Trials Unit (DIAN-TTU) will assess three drugs in

“We are grateful for the chance to evaluate such a promising prevention treatment. We have tried to design the study in a way that might bring the field closer to ending Alzheimer's before another generation is lost.”

Eric Reiman, MD.
Executive Director, Banner Alzheimer’s Institute
asymptomatic subjects with AD-associated mutations in the presenilin 1, 2, or amyloid precursor protein genes. The trial is to start by early 2013, and in October 2012, it was announced that solanezumab, gantenerumab, and LY-2886721, a beta secretase inhibitor from Eli Lilly, had been chosen as the three drugs to be investigated. The beta secretase enzyme cleaves amyloid precursor protein at the beta site, and is essential for the production of Abeta. In a phase I trial, LY-2886721 was shown to reduce CSF Abeta levels. Phase II trials are underway, with data expected from 2014.

The biochemical information gained from DIAN is also likely to help with the development of other AD therapeutics, by providing information on the pathology of the disease and also ways to spot non-genetically-linked AD cases much sooner in the progression of the disease, thus enabling earlier treatment. Data published in July 2012 showed that in genetically linked AD, Abeta levels in cerebrospinal fluid (CSF) begin to drop 25 years before the expected age of AD onset. At five years before expected onset global cognitive impairment appeared, and diagnostic criteria for dementia were met an average of three years after the expected age of AD onset.

DIAGNOSTIC AGENTS

Measuring brain Abeta levels in the DIAN study was performed using Pittsburgh compound B (PIB), which binds Abeta, as an imaging agent during positron emission tomography (PET) scans of the brain. However, this agent is not ideal for widespread commercial use for diagnosing AD due to the short half-life of its radionuclide element, carbon 11 (11C), which necessitates access to an on-site cyclotron and radiochemistry laboratory. The recent commercial launch of Avid Radiopharmaceuticals and Eli Lilly’s Amyvid, the first Abeta imaging agent to use the more stable fluorine 18 (18F) radionuclide element which can be produced at central cyclotron sites for delivery to local PET facilities, will further enhance the value of AD diagnostic agents as facilitators of improved therapeutic development.

The launch of diagnostics such as Amyvid will maximize the value of AD drugs, by providing a commercially available tool to more accurately diagnose the presence of the disease in any given patient, and thus treat them appropriately. Avid’s President and CEO, Daniel Skovronsky, noted: “It’s estimated that one in five patients clinically diagnosed with probable AD during life do not end up having AD pathology upon autopsy.” The disease is currently diagnosed using a mix of physical examinations, tests and assessments of cognitive ability, which may be subjective. Furthermore, current tests can only pick up the disease once a decline in cognitive function has begun, whereas Abeta imaging has the potential to detect AD in its early stages, when Abeta deposition has begun but before dementia symptoms start, thus giving the opportunity of initiating treatment much earlier and

“Improving detection technologies and updated diagnostic guidelines are enabling the detection of early changes in the brain and subtle cognitive deficits that are consistent with what is now known as presymptomatic (or preclinical) Alzheimer’s. People in this stage of the disease are an ideal population for prevention trials to delay the onset or slow the progression of cognitive decline.”

William Thies, PhD.
Chief Medical and Scientific Officer, Alzheimer’s Associations
potentially with greater efficacy. It has been estimated that early
diagnosis and treatment may save $10,000 over the lifetime of
each dementia patient, for example by delaying the need for
institutional care.

Measuring Abeta deposition in parallel to measuring traditional
markers such as cognitive function could also help elucidate the
pathology behind the disease. Measuring Abeta levels before,
during and after treatment would also provide an extra way of
assessing drug efficacy. The ability to determine a given patient’s
Abeta levels also provides the opportunity for more specific
patient selection for trials and treatment, thus refining and
improving the targeting of AD therapy. It has been estimated
that the value of the global AD diagnostic market is between
$1 billion and $5 billion, although the current non-coverage of
new PET agents by Medicare may hamper uptake.

Amyvid was approved by the FDA in April 2012 for use in
diagnosing or ruling out a diagnosis of AD, and was launched
in June. It does not replace other diagnostic methods, but can
be used to supplement them. In a phase III trial comparing
Amyvid images with subsequent autopsies, data showed that
the imaging results correlated with Abeta pathology found
at autopsy. In two other studies, the median sensitivity and
specificity of Amyvid was 92 and 95 percent, respectively, for
readers trained in person, and 82 and 95 percent, respectively,
for readers trained using an electronic media-based training. A
condition of approval of the agent was the establishment of a
reader training program.

Closely behind Amyvid in the diagnostics development pipeline
is GE Healthcare’s flutemetamol (18F), an 18F-labeled derivative
of PIB that is expected to be filed for approval later in 2012.
Phase III data showed concordance between flutemetamol (18F)
PET images and AD-associated Abeta brain pathology seen at
autopsy, while young healthy subjects were shown to lack brain
Abeta. Although Amyvid has first-to-market advantage, GE
plans to gain an edge over its competitor by providing a package
of imaging tools rather than just one agent. It is developing
software to facilitate analysis of the flutemetamol (18F) scans,
and plans to launch the Abeta diagnostic alongside magnetic
resonance imaging (MRI) scanning to assess brain volume, which
also changes as the disease progresses.

Also close on the heels of Amyvid is Piramal Healthcare’s
florbetaben (18F), which, like flutemetamol (18F), recently
produced phase III results and is to be filed this year. The phase
III data showed that the visual assessment procedure proposed
for routine clinical use of the agent gave sensitivity and specificity
of 100 and 92 percent, respectively. Piramal, which acquired
Bayer’s molecular imaging portfolio including florbetaben (18F) in
April 2012, anticipates that revenue from florbetaben (18F) could
potentially reach $1.5 billion. The diagnostic market, as well as the
therapeutic one, is therefore a lucrative one, but its full potential
has to date been limited by the lack of funding for AD.
AN INFLUX OF NEW FUNDING

Developments in the early treatment of AD and in its diagnosis are not the only game-changing events in the AD field in recent months. In May 2012, the US Government launched the National Alzheimer’s Plan (NAP), which has a budget of $156 million in this year and next. It brings much needed funding to a previously cash-poor condition, and may help to make the area more attractive for increased pharmaceutical industry involvement. The first goal of the NAP is to effectively prevent and treat AD by 2025. This is by far the biggest part of the funding commitment, with $50 million earmarked in 2012, and a further $80 million in 2013. The NAP’s four other goals are to optimize AD care quality and efficiency, to expand the support available for AD patients and their families, to increase public awareness and engagement, and to enhance the Government’s ability to track its progress against the disease. Optimizing AD care has been allocated $6 million over two years, AD support is to get $10.5 million in 2013, public awareness will receive $8.2 million over two years, and progress tracking is to cost $1.3 million in 2013. One of the first two research programs to receive funds from the NAP was the Colombian crenezumab study, which was awarded $16 million. The second grant was $7.9 million for a trial assessing AD treatment with an insulin nasal spray, which raises a very different theory of AD pathology and treatment.

A POSSIBLE LINK TO INSULIN

The targeting of Abeta has been the central tenet of many AD therapeutics in development, but recently an alternative paradigm has been put forward, raising the possibility of a completely different way to attack AD. A potential link between AD and insulin is being investigated, although the idea is still in its infancy.

It has been shown that being diabetic increases a person’s risk of developing AD. Why this is so has not been conclusively determined, but additional links exist between the two diseases. Defects in protein processing, insulin signalling, glucose metabolism and even cognitive function are examples of common features. Given these links, it is worth investigating whether the treatments that work for diabetes may also work for AD. An increasing number of studies are looking into this possibility.

Data published in January this year from the phase II, randomized, double-blind, 104-patient, SNIFF 120 trial showed that nasal administration of insulin for 16 weeks improved delayed memory and preserved caregiver-rated functional ability in patients with either mild cognitive impairment (MCI) or AD. In AD patients, the insulin also preserved functional abilities as assessed by ADCS-ADL score. Exploratory analyses showed that memory and function changes were associated with changes to Abeta levels and to the CSF tau protein-to-Abeta ratio. The
Another diabetes drug being repurposed for AD is Novo Nordisk’s liraglutide – an analog of glucagon-like peptide-1 (GLP-1), which is a protein involved in normal glucose metabolism. GLP-1 has also been shown to reduce Abeta production and to be neuroprotective. The Alzheimer’s Society recently funded a three-year trial into the effects of liraglutide on AD patients at Imperial College London. Cerebral inflammation and glucose metabolism and spinal Abeta and tau levels will be assessed.

A number of pharmaceutical companies are also assessing their diabetes drugs for utility against AD. Takeda is conducting a phase I AD-prevention trial of its thiazolidinedione PPAR-gamma agonist, pioglitazone, having completed a phase II trial in AD patients in 2005. GlaxoSmithKline had taken an extended-release formulation of its PPAR-gamma agonist thiazolidinedione, rosiglitazone, into phase III trials for AD, but suspended development in 2009 due to lack of efficacy. Interestingly, Metabolic Solutions Development has recently postulated that the positive effects of this type of drug are due not to their PPAR-gamma activity, but to modulation of a mitochondrial protein complex. The complex, termed the mitochondrial target of thiazolidinediones (mTOT), connects mitochondrial metabolism to the cellular metabolism of carbohydrates, lipids, and amino acids. The company has just completed a phase IIa AD trial of its mTOT modulator, MSDC-0160, which it is also assessing as a diabetes treatment. Data are expected soon.

CONCLUSION I

As patent expirations impact the future revenues of the major AD treatments, recent events in the field, both positive and negative, highlight just how dynamic this area remains. There has been a high rate of attrition in the drug pipeline, but also some promising candidates taking their place. New studies into the optimal timing of treatment promise greater insights into the disease and potentially open up new ways to try to treat it. New imaging agents will enable better diagnosis and further enhance the drug discovery process, while an influx of new funding will hopefully invigorate research into this cash-strapped condition. The Abeta hypothesis of AD causation retains traction despite recent knocks, and a new link to insulin offers extra options for research.
SECTION II
DEALS HIGHLIGHTS

Deals coverage from Cortellis for Competitive Intelligence indicates that more than 660 deals related to AD have been forged since the mid 1980s.

The following section reviews the licensing portfolio of a number of AD drugs on the market, as well as certain significant and promising therapeutic candidates for the indication, as featured in Cortellis for Competitive Intelligence. Other notable and high-value deals are also highlighted to give an insight into the AD market.

NAMENDA: PROLIFIC PARTNERING ACTIVITY

Merz & Co’s launched AD therapeutic Namenda is notable for the high number of deals that have been forged during its development and commercialization, deals spanning the US, Japan and the rest of the world. In contrast, Novartis’s Exelon, another established AD drug on the market, appears to have little partnering activity. Only a Japanese codevelopment agreement with Ono Pharmaceutical, of unknown financial worth, for a transdermal formulation (Exelon TDS) is covered on Cortellis for Competitive Intelligence.

In the US, Neurobiological Technologies Inc (NTI) acquired rights from the Children’s Hospital Boston to certain patents related to Namenda in 1995 (financial terms were undisclosed). However, in April 1998, the Children’s Hospital Boston’s Children’s Medical Center Corp (CMCC) terminated the agreement; NTI and CMCC then exclusively granted the rights to Merz, and established a revenue sharing partnership.

The resulting deal between NTI and Merz generated revenues for NTI of more than $35 million over a decade. Merz replaced NTI as licensee of the patents and agreed to pay its partners a share in revenues from worldwide sales (excluding Japan, Korea, China, Germany, Italy, Spain, several smaller European countries, and a large portion of Latin America; all markets with pre-existing agreements) of the therapeutic for AD, AIDs-related dementia, and neuropathic pain. Merz paid NTI a $2.1 million upfront payment, and in 2000 Merz’s agreements for the drug with Forest Laboratories and Lundbeck initiated revenue sharing including milestones of at least $7.7 million, significant royalties and a $2.5 million upfront payment to NTI. NTI continued to receive significant milestone payments and royalties until the
license and cooperation came to an end in August 2009. To satisfy its royalty and other obligations, Merz made a termination payment to NTI, which along with a royalty payment due, totaled approximately $6 million. Both companies mutually released all claims related their agreement.

Forest Laboratories acquired from Merz exclusive US development and comarketing rights for Namenda in June 2000. The deal, of undisclosed financial terms, is due to expire in 2028 and covers AD, neuropathic pain and other CNS indications.

In Japan, Suntory licensed rights to the drug from Merz in 1998, and by March 2002, Daiichi Pharmaceuticals had agreed to conduct joint AD trials of Namenda with Suntory. Under the terms of that agreement, once the product was approved, it would be manufactured by Suntory and marketed by Daiichi. In January 2003, Daiichi Suntory Pharma took over Suntory’s pharmaceutical activities, including the Japanese development for Namenda. Later, in September 2005, Daiichi Suntory Pharma (now Asubio Pharma) became a wholly owned subsidiary of Daiichi Seiyaku (now Daiichi Sankyo). Financial terms for these agreements were undisclosed.

In certain European markets, Canada, Australia, and South Africa, Merz granted Lundbeck exclusive Namenda rights in August 2000, covering AD, vascular dementia, neuropathic pain, and AIDS-related dementia. Lundbeck was also granted semi-exclusive comarketing rights in the remaining worldwide territories, excluding the US and Japan. Lundbeck signed a Korean copromotion agreement for the drug with Hanmi Pharmaceutical in November 2009. The companies agreed to comarket Namenda from the beginning of 2010 for five years. Financial terms for the agreements were undisclosed. Namenda is also covered by deals for specific indications other than AD.

“We believe Memantine (Namenda) is an immensely useful and versatile drug which will be very helpful for many people. We are delighted to enter into this relationship with Merz which has a leading research program in CNS and particularly in the field of N-methyl-D-aspartate (NMDA) antagonists.”

Howard Solomon.
Chairman and CEO, Forest Laboratories
TABLE 1: SUMMARY OF NAMENDA’S AGREEMENTS

* Approximate values based on the achievement of all milestones for the principal components included in the deal.

PARTNERING PORTFOLIO FOR RAZADYNE AND ARICEPT

Other established AD drugs Razadyne and Aricept also demonstrate healthy partnering activity. Shire Pharmaceuticals and Janssen Pharmaceutica acquired global manufacture and supply rights to Razadyne in June 1997 from Waldheim Pharmazeutika (now Sanochemia Pharmazeutika), who had originally discovered a synthetic version of the alkaloid. In exchange for $1 million, Shire acquired rights to the Nivalin (Waldheim’s older version of the drug) trademark. Shire and Janssen were also granted exclusive access to the patented synthetic manufacturing processes and technologies of Waldheim, and Waldheim agreed to supply the drug in finished form for Janssen to sell in Austria and certain East European markets. Shire and Janssen had previously licensed (by June 1997) rights to the use of the compound for the treatment of AD disease under patents held by Synaptech. In exchange, Synaptech would receive royalties on ex-Japanese sales. Shire and Janssen also entered a copromotion agreement for the drug by March 1999. Shire held marketing rights in the UK and Ireland and received royalties from Janssen sales in other markets.

Other deals for Razadyne include Janssen and Biofrontera Pharmaceuticals’ research collaboration to explore the potential benefits of ‘nicotinic modulation’ in the treatment of AD in August 2001, and Takeda Pharmaceutical’s March 2010 deal to comarket the drug in Japan with Janssen. Takeda agreed to pay Janssen an undisclosed upfront payment, a launch milestone, annual sales-based milestones and a fixed rate on sales.
Eisai’s AChE inhibitor Aricept was codeveloped with Pfizer under a November 1995 agreement to develop AD therapeutics worldwide. The companies agreed to comarket Aricept in the US, the UK, Germany, and France, with Pfizer retaining exclusive marketing rights in all other territories outside Asia, Latin America, and Italy. Pfizer Seiyaku and Eisai would also comarket in Japan (financial details were undisclosed). An amendment to the deal was made in September 2009, namely that the companies would continue their copromotion activities in the US, Japan, and key European markets. The deal was to expire on December 31, 2012. Wyeth-Ayerst International (now Pfizer following its acquisition of Wyeth in 2009) also acquired exclusive Latin American marketing rights in 1995.

Other deals for Aricept include an agreement in which Catalytica agreed to manufacture the drug for Pfizer signed by December 1996. Cardinal Health agreed to be the distributor of Eisai’s US products including Aricept by January 2005, although the agreement was terminated that year since a suitable arrangement had failed to be reached. Also, it appears that Eisai had agreed for Daewoong Pharmaceutical to market Aricept in Korea by April 2010. Financial terms for all these agreements were undisclosed.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>LICENSING COMPANY</th>
<th>PARTNER COMPANY</th>
<th>DEAL START DATE</th>
<th>DEAL VALUE (US $)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Razadyne</td>
<td>Waldheim Pharmazeutika</td>
<td>Shire</td>
<td>June 1997</td>
<td>&gt;1 million</td>
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<td>Razadyne</td>
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<td>Janssen Pharmaceutica</td>
<td>June 1997</td>
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<td>Razadyne</td>
<td>Synaptec</td>
<td>Shire</td>
<td>By June 1997</td>
<td>Royalties</td>
</tr>
<tr>
<td>Razadyne</td>
<td>Synaptec</td>
<td>Janssen Pharmaceutica</td>
<td>By June 1997</td>
<td>Royalties</td>
</tr>
<tr>
<td>Razadyne</td>
<td>Janssen Pharmaceutica</td>
<td>Shire</td>
<td>By March 1999</td>
<td>Royalties</td>
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<td>Janssen Pharmaceutica</td>
<td>August 2001</td>
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<td>Razadyne</td>
<td>Janssen Pharmaceutica</td>
<td>Takeda Pharmaceuticals</td>
<td>March 2010</td>
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</tr>
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<td>Aricept</td>
<td>Eisai</td>
<td>Pfizer</td>
<td>November 1995</td>
<td>Undisclosed</td>
</tr>
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<td>Aricept</td>
<td>Eisai</td>
<td>Wyeth-Ayerst</td>
<td>1995</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>Aricept</td>
<td>Catalytica</td>
<td>Pfizer</td>
<td>By December 1996</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>Aricept</td>
<td>Eisai</td>
<td>Cardinal Health</td>
<td>By January 2005</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>Aricept</td>
<td>Eisai</td>
<td>Daewoong Pharmaceutical</td>
<td>By April 2010</td>
<td>Undisclosed</td>
</tr>
</tbody>
</table>

**TABLE 2: SUMMARY OF RAZADYNE AND ARICEPT AGREEMENTS**

* Approximate values based on the achievement of all milestones for the principal components included in the deal.
**CRENEZUMAB DEAL PROFILE**

Roche’s wholly owned subsidiary Genentech is currently developing the phase II anti-Abeta-amyloid mAb, crenezumab, under license from AC Immune. Genentech acquired exclusive worldwide rights in December 2006, agreeing to pay AC Immune an upfront payment, and over $300 million in milestones, plus royalties. Genentech paid its second milestone in May 2011 when the first patient was dosed in phase II AD trials. Roche acquired an opt-in opportunity to develop crenezumab in January 2009 for undisclosed financial terms. The antibodies for the program are manufactured by DSM Biologics, who was contracted by AC Immune in March 2006.

The API trial of crenezumab announced in May 2012 with Genentech, Banner Alzheimer’s Institute, University of Antioquia, and the NIH is worth $100 million. The NIH awarded a five-year $16 million grant for the study and the Banner Alzheimer’s Institute committed $15 million in philanthropic funds. The major share of funding for the trial would come from Genentech.

**TABLE 3: SUMMARY OF CRENEZUMAB’S AGREEMENTS**

* Approximate values based on the achievement of all milestones for the principal components included in the deal.

<table>
<thead>
<tr>
<th>LICENSING COMPANY</th>
<th>PARTNER COMPANY</th>
<th>DEAL START DATE</th>
<th>DEAL VALUE (US $)*</th>
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<tr>
<td>AC Immune</td>
<td>Genentech</td>
<td>December 2006</td>
<td>&gt;300 million</td>
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<tr>
<td>AC Immune</td>
<td>Roche</td>
<td>January 2009</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>DSM Biologics</td>
<td>AC Immune</td>
<td>March 2006</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>Genentech</td>
<td>NIH</td>
<td>May 2012</td>
<td>16 million</td>
</tr>
<tr>
<td>University of Antioquia</td>
<td>Genentech</td>
<td>May 2012</td>
<td>Undisclosed</td>
</tr>
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</table>

**ELI LILLY AND THE DEVELOPMENT OF ALZHEIMER’S DISEASE THERAPIES**

The deal landscape for AD is well covered by the big Pharma players with Eli Lilly’s presence clearly established.

Eli Lilly was developing the gamma secretase inhibitor semagacestat until phase III trials were halted in August 2010. The company had established a research alliance with Athena Neurosciences (now Elan Pharmaceuticals) in 1988 to discover and develop AD therapeutics, including semagacestat. The companies amended their collaboration in June 1995, reinforcing equal ownership of a transgenic mouse model for AD. Eli Lilly would increase funding to support Athena’s research efforts in the field. The alliance was extended through to August 1998 in February 1997. On ending the collaboration in 1998, Eli Lilly was granted an exclusive worldwide license under certain patents to make, use and sell any compound owned by Elan and discovered during their alliance. Elan retained certain commercial rights under the agreement.

The company is also developing anti-Abeta mAb solanezumab, although primary endpoints in two phase III trials were not met, and in October 2012, Eli Lilly was reportedly determining...
the development plan for the drug following discussions with regulatory agencies. PDL BioPharma had non-exclusively licensed to Eli Lilly certain patents related to solanezumab and the anti-diabetes mAb teplizumab by December 2009. The company receives royalties on sales of its humanized antibody products and would continue to do so until patent expiry in late 2014.

The beta secretase inhibitor (BACE) LY-2886721 is currently being developed by Eli Lilly and has reached phase II trials in the US and Japan.

Takeda Pharmaceutical’s PPAR-gamma agonist and insulin sensitizer pioglitazone is co-marketed by Eli Lilly in a number of worldwide territories. By June 1998, the companies were copromoting the drug in the US. In August 1999, the agreement was expanded to give Eli Lilly marketing rights in more than 70 countries within Europe, the Middle East, Africa, and the Asia Pacific (excluding Japan) region. Takeda regained US sales and marketing rights in April 2006, and Canadian commercial rights in August 2009. Financial terms were undisclosed.

Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly (following Eli Lilly’s acquisition of Avid in December 2010), gained rights from the University of Pennsylvania to beta-amyloid-binding 18F PET imaging agents, Amyvid and florbetaben (18F) by January 2005. Financial terms were undisclosed. Avid received a share of a $1.9 million grant from the Michael J Fox Foundation to support development of its 18F-labeled alpha-synuclein ligands for PET imaging of Lewy bodies in February 2009. Avid also entered manufacturing agreements with Cardinal Health and Siemens Medical Solutions’ subsidiary PETNET Solutions for PET imaging agents. Schering (now Bayer) gained an exclusive option to develop and commercialize Avid’s amyloid binding compounds for the diagnosis of AD in December 2005. The option covered 18F-stilbene PET imaging agents and financial details were undisclosed. Bayer exercised the option in June 2007 to gain exclusive rights to florbetaben (18F).

“Our expanded agreement with Takeda enables both companies to help optimize the full potential value of Actos and compete effectively within the oral hypoglycemic market.”

Sidney Taurel.
Chairman, Former CEO, Eli Lilly

<table>
<thead>
<tr>
<th>LICENSING COMPANY</th>
<th>PARTNER COMPANY</th>
<th>DEAL START DATE</th>
<th>DEAL VALUE (US $)*</th>
</tr>
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<tbody>
<tr>
<td>Eli Lilly</td>
<td>Athena Neurosciences</td>
<td>1998</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>PDL BioPharma</td>
<td>Eli Lilly</td>
<td>December 2009</td>
<td>Royalties</td>
</tr>
<tr>
<td>Takeda Pharmaceutical</td>
<td>Eli Lilly</td>
<td>By June 1998</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>Avid Radiopharmaceuticals</td>
<td>By January 2005</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>Avid Radiopharmaceuticals</td>
<td>Michael J Fox Foundation</td>
<td>February 2009</td>
<td>&lt;1.9 million</td>
</tr>
<tr>
<td>Cardinal Health</td>
<td>Avid Radiopharmaceuticals</td>
<td>By March 2010</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>Siemens Medical Solutions</td>
<td>Avid Radiopharmaceuticals</td>
<td>By April 2010</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>Avid Radiopharmaceuticals</td>
<td>Schering</td>
<td>December 2005</td>
<td>Undisclosed</td>
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</table>

**TABLE 4: SUMMARY OF ELI LILLY’S AGREEMENTS**

* Approximate values based on the achievement of all milestones for the principal components included in the deal.
HIGH VALUED DEALS FOR ALZHEIMER’S DISEASE

The highest valued deals related to AD as reported on Cortellis for Competitive Intelligence is J&J’s acquisition of Elan’s Alzheimer’s Immunotherapy Program (AIP) for up to $1.358 billion in July 2009. J&J, through the newly formed company Janssen Alzheimer Immunotherapy, acquired Elan’s assets and rights related to the AIP program, which included AN-1792, bapineuzumab, AAB-002, ACC-001, ACC-002, and anti-amyloid beta antibody vaccines. J&J would also invest $1 billion in Elan for American Depositary Receipts (ADRs) representing 18.4 percent of Elan’s outstanding ordinary shares. The AIP was formed in April 2000 with Wyeth; J&J would assume and continue Elan’s activities with Wyeth. Initially, J&J would provide up to $0.5 billion to continue development and launch of the drugs. An equity interest in the new company of 49.9 percent would be held by Elan, giving it rights to 49.9 percent of profits and certain royalties. In September 2009, J&J amended the agreement by only investing $885 million and not $1 billion in Elan to cure an unintentional breach of its Tysabri collaboration with Biogen. The deal, which had been subject to closing conditions, closed in September 2009.

Another high valued deal for AD was Pfizer and Medivation’s September 2008 collaboration for the development of Dimebon, worth more than $725 million. The companies agreed to codevelop the drug in the US, and Pfizer was granted exclusive rights outside the territory, in exchange for a $225 million upfront payment, up to $500 million in developmental and regulatory milestone payments and undisclosed commercial milestones. Costs in the US would be shared 60:40 (Pfizer: Medivation). By October 2009, the companies were codeveloping a transdermal formulation of the drug. However, the agreement terminated in January 2012 following disappointing results in a phase III trial, and it was unclear if the transdermal formulation was also affected.

“This transaction will leverage Elan’s unique scientific and clinical work and leadership in bringing treatments to market that potentially slow the progression of Alzheimer’s disease.”

Kelly Martin.
CEO, Elan

“After a rigorous process that garnered substantial interest, we believe that Pfizer is the ideal partner, sharing our vision for Dimebon and capable of maximizing its potential globally.”

David Hung.
President and CEO, Medivation
<table>
<thead>
<tr>
<th>DRUG</th>
<th>LICENSING COMPANY</th>
<th>PARTNER COMPANY</th>
<th>DEAL START DATE</th>
<th>DEAL VALUE (US $)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN-1792, bapineuzumab, AAB-002, ACC-001, ACC-002, anti-amyloid beta antibody vaccines</td>
<td>Elan</td>
<td>Johnson &amp; Johnson</td>
<td>July 2009</td>
<td>&lt;1385 million</td>
</tr>
<tr>
<td>Dimebon</td>
<td>Medivation</td>
<td>Pfizer</td>
<td>September 2008</td>
<td>&gt;725 million</td>
</tr>
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</table>

TABLE 5: SUMMARY OF HIGH VALUED AGREEMENTS FOR ALZHEIMER’S DISEASE

* Approximate values based on the achievement of all milestones for the principal components included in the deal.

CONCLUSION II

On observing the deal landscape for AD it is clear this is a market of interest to companies seeking partnerships, as indicated by the large and wide number of deals recorded, and the healthy partnering portfolios for prominent AD therapeutics and therapeutic candidates. Eli Lilly is just one of a number of Pharma giants with an established presence in the field. However, as already established, the indication does not attract as much research funding as other diseases; only around 100 funding deals are recorded on Cortellis for Competitive Intelligence, with only approximately ten grants recorded in 2012. With the US Government’s pledge of $130 million for Alzheimer’s R&D, we can expect to see a substantial rise in the number of these funding deals and subsequent increased Pharma partnering in the coming years.
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