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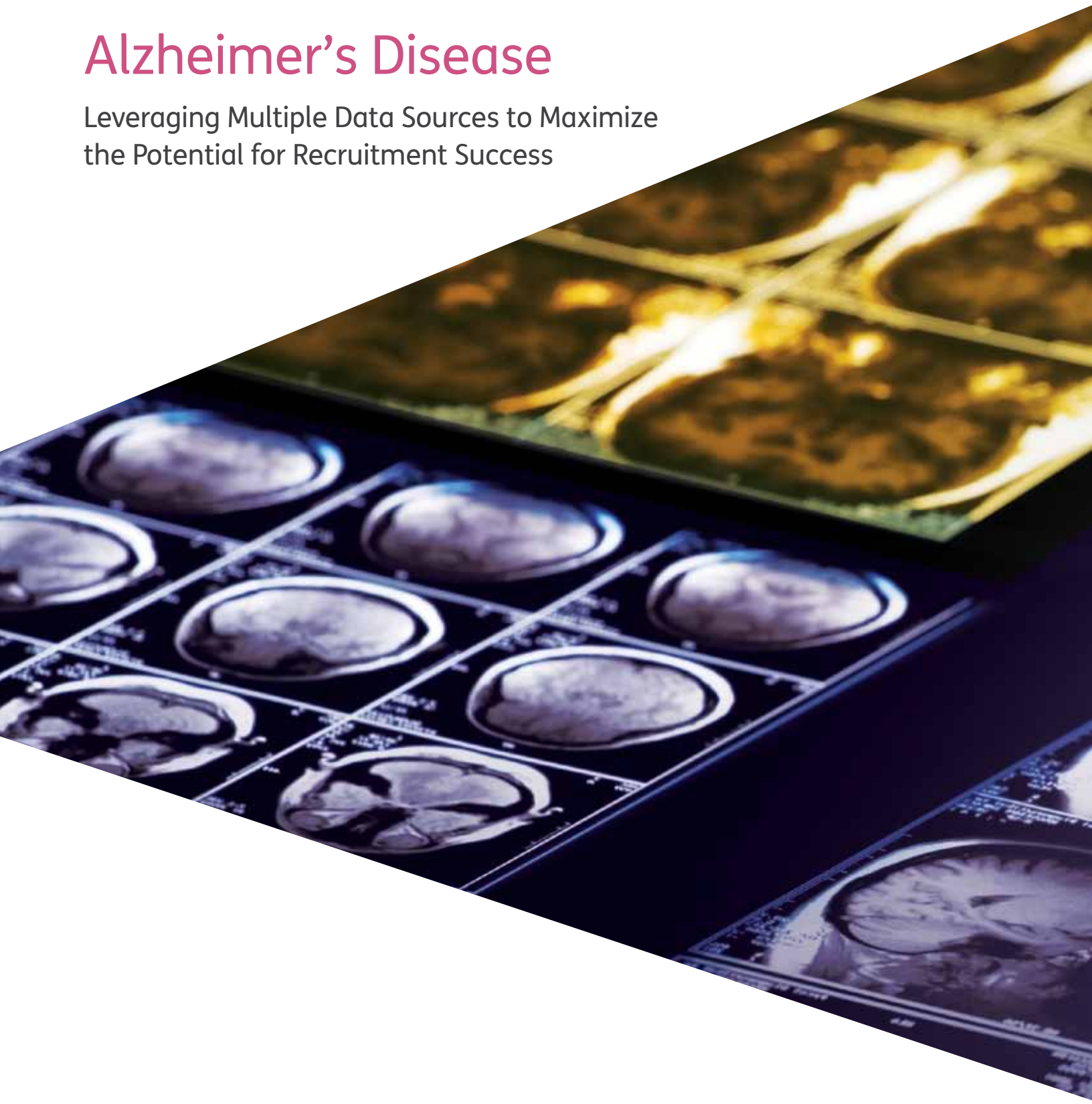
Alzheimer's Disease

Leveraging Multiple Data Sources to Maximize the Potential for Recruitment Success



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Leveraging Multiple Data Sources to Maximize the Potential for Recruitment Success in Alzheimer's Disease

Alzheimer's Disease (AD) is the most common form of dementia, and accounts for 60% to 80% of dementia cases. In this progressive disease, dementia symptoms gradually worsen over a number of years. Memory loss is mild during early stages, but individuals with late-stage Alzheimer's lose the ability to carry on a conversation and respond to their environment. The greatest known risk factor is increasing age, and the majority of people with Alzheimer's are 65 and older. That said, up to 5% of people with the disease have early onset Alzheimer's, which often appears when someone is in their 40s or 50s[1]. Studies indicate that people aged 65 and older survive an average of four to eight years after diagnosis of Alzheimer's disease, yet some live as long as 20 years or more, demonstrating the slow, insidious progression of the disease[2].

[1] *Alzheimer's Association: http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp*

[2] *Datamonitor Healthcare: https://service.datamonitorhealthcare.com/hkc/disease/central-nervous-system/neurology/alzheimers-disease/epidemiology/article143160.ece*

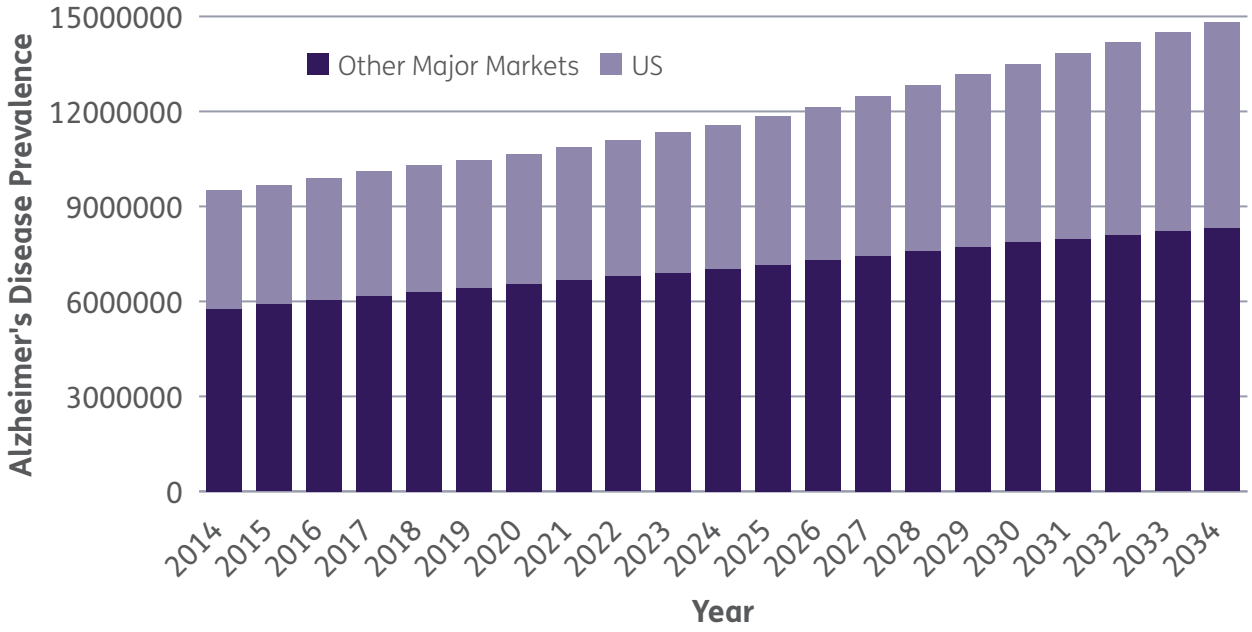
The prevalence of Alzheimer's continues to grow and poses a critical public health problem. All approved Alzheimer's treatments address symptoms alone and not the neurodegeneration of the disease. Accelerated clinical research is needed for hopes of identifying a successful disease-modifying treatment option. By integrating multiple data sources to assess clinical trial and drug landscapes, disease prevalence, and top investigators and sites, one can ensure the greatest potential for clinical trial success.

9.5

million estimated numbers of prevalent cases of Alzheimer's disease in the 7 major markets in 2014

The number of drugs in development for Alzheimer's is at an all-time high, and features various modes of action with a significant Big Pharma presence. The introduction of biomarkers makes the diagnosis of Alzheimer's disease in the mild cognitive impairment and pre-symptomatic stages a distinct possibility, facilitating a shift in the future treatment landscape toward preventative interventions. This much needed shift towards preventative interventions could not come at a better time as Datamonitor Healthcare® forecasts growth in Alzheimer's disease prevalence through 2034 across the 7 major markets (7MM) of the US, Japan France, Germany, Italy, Spain, and UK. In 2014, there were an estimated 9.5 million prevalent cases of Alzheimer's disease in the 7MM, which is forecasted to increase to 14.8 million by 2034[2]. [Figure 1]

Figure 1: Forecasted Growth in Disease Prevalence



Source: Datamonitor Healthcare®, November 2015

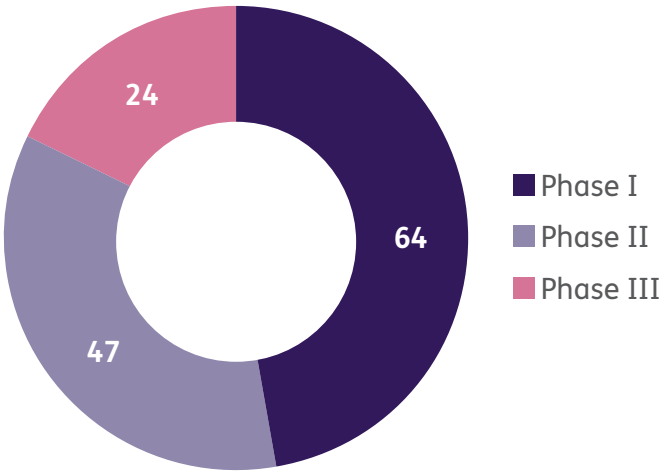
What is in the Pipeline?

Currently, there is no cure for Alzheimer's disease and approved treatment options are either acetylcholinesterase inhibitors (Aricept, Exelon, and Razadyne) or a NMDA antagonist (Namenda), all of which treat the symptoms of the disease only. A shift in focus to therapeutic treatment, also called disease-modifying drugs, has increased with several disease-modifying drugs in late stages of clinical development. Disease-modifying drugs could slow the neurodegeneration associated with disease progression and significantly benefit patients by improving clinical outcomes. Furthermore, this may extend the life expectancy of Alzheimer's disease patients. Unfortunately, development of this class of drugs remains the number one unmet need in the market[3].

[3] *Datamonitor Healthcare: https://service.datamonitorhealthcare.com/disease/central-nervous-system/neurology/alzheimers-disease/*

Pharmaprojects® shows a high volume of drugs in the pipeline for Alzheimer's, with over 70 in mid-to-late stage development. Many are disease-modifying drugs, such as Merck's MK-8931, Chiesi's CSP-1103, and Lilly's solanezumab[4]. Solanezumab may be the first disease-modifying drug for managing the treatment of Alzheimer's as it has shown modest improvements on memory and thinking in people with mild Alzheimer's[5]. [Figure 2]

Figure 2: Alzheimer's Disease Drug Landscape Phases I-III



Source: Pharmaprojects®, December 2015

[4] *Alzheimer's Association: http://www.alz.org/research/science/alzheimers_treatment_horizon.asp*
[5] *Alzheimer's Research UK: http://www.dementiablog.org/solanezumab/*

The top six mechanisms of action (MOA) for the current Alzheimer's drug landscape are outlined in Figure 3, which shows beta amyloid as a prime target. This protein forms plaques in the brain that disrupts brain cells by blocking cell to cell communication, activating immune cells that trigger inflammation and eventually killing cells. Beta amyloid protein and precursor protein antagonists would block the effects of beta-amyloid[6]. Currently, both are top MOAs with 20 and 7 drugs in the pipeline, respectively. Although three acetylcholinesterase inhibitors have already been approved and generic options are available, it remains a top MOA with 7 pipeline drugs. These drugs prevent the breakdown of acetylcholine in the brain, a chemical messenger important for learning and memory. Acetylcholinesterase inhibitors support communication among nerve cells by keeping acetylcholine levels high[7].

20
beta amyloid protein antagonists in the pipeline

7
precursor protein antagonists in the pipeline

Figure 3. Top Mechanisms of Action for Alzheimer's Disease Drug Landscape Phases I-III

Top Mechanisms of Action	No. of Drugs
Beta amyloid protein antagonist	20
5 HT6 receptor antagonist	8
Tau aggregation inhibitor	7
Secretase beta (BASE) inhibitor	7
Beta amyloid precursor protein antagonist	7
Acetylcholinesterase inhibitor	7

Source: Pharmaprojects®, December 2015

[6] *Alzheimer's Association: https://www.alz.org/national/documents/topicsheet_betaamyloid.pdf*
[7] *Alzheimer's Association: http://www.alz.org/alzheimers_disease_standard_prescriptions.asp*

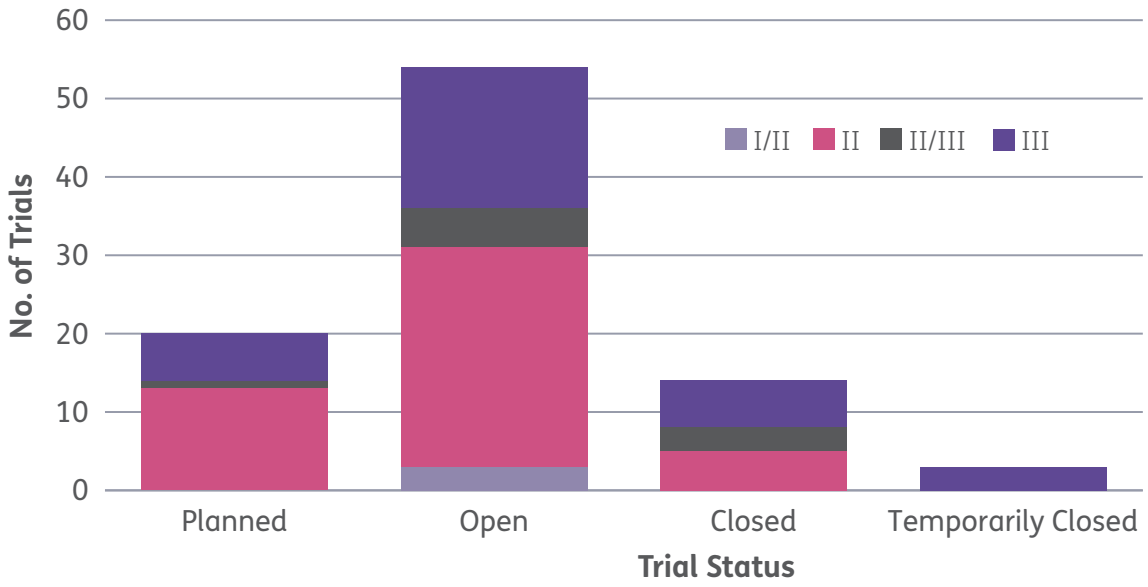
The Trial Landscape

90+

active* Phase I/II-III Industry sponsored trials involving early stage Alzheimer's patients

In the earliest stages of Alzheimer's disease, subtle cognitive deficits may be evident only through the use of sensitive neuropsychological assessments. Before manifesting into dementia, patients proceed through a clinical phase where cognition becomes increasingly affected and relatively mild but detectable impairments in some functional abilities are seen (sometimes referred to as mild cognitive impairment (MCI)). The development of drugs to treat Alzheimer's has increasingly focused on this entire range of disease states that occur before the onset of overt dementia because the benefits of a disease-modifying therapy are presumed to be the greatest in these stages[8]. Therefore, early stage Alzheimer's disease research is imperative. According to Trialtrove®, there are over 90 active* Phase I/II-III Industry sponsored trials involving early stage Alzheimer's patients. The majority of this trial activity is primarily phase II. [Figure 4]

Figure 4: Active* Trials for Early Stage Alzheimer's by Phase & Status

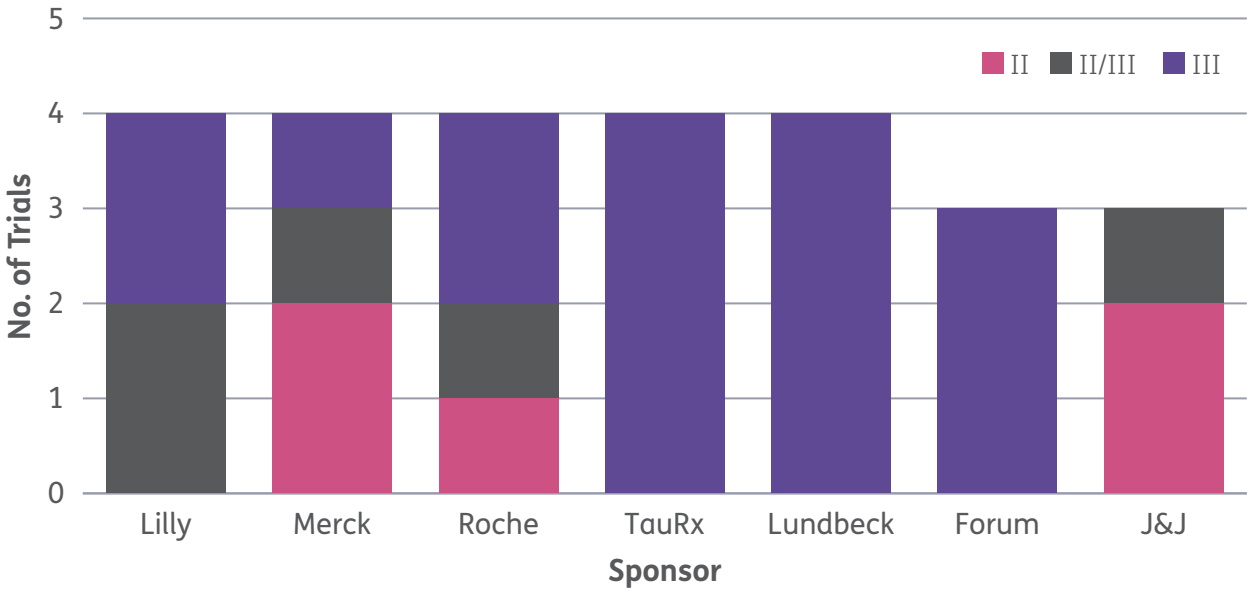


*Active trial refers to any planned or ongoing early Alzheimer's Disease trial.
Source: Trialtrove®, December 2015

[8] *"Guidance for Industry Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease": http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338287.pdf*

Among sponsors with three or more active trials, five of the seven companies have four active early stage Alzheimer's trials (Eli Lilly, Merck, Roche, TauRx, and Lundbeck). [Figure 5] Lilly, partnered with Roche, has one phase II/III trial involving beta amyloid protein antagonists, solanezumab and gantenerumab. Solanezumab is under evaluation in two additional phase III studies, and Lilly is also evaluating a secretase beta inhibitor, AZD-3293 (phase II/III). Roche has an additional phase III gantenerumab trial as well as two crenezumab studies (phases II and III), another beta amyloid protein antagonist. The remaining sponsors are pursuing various targets besides the popular beta amyloid protein. TauRx's four active phase III trials all evaluate their tau inhibitor, leuco-methylthioninium. Lundbeck has three active phase III trials involving 5 HT6 receptor antagonist, idalopirdine, and one phase III trial involving dopamine D2 receptor agonist, brexpiprazole. Lastly, two of Merck's four active trials evaluate their secretase inhibitor, MK-8931 (phases II/III and III).

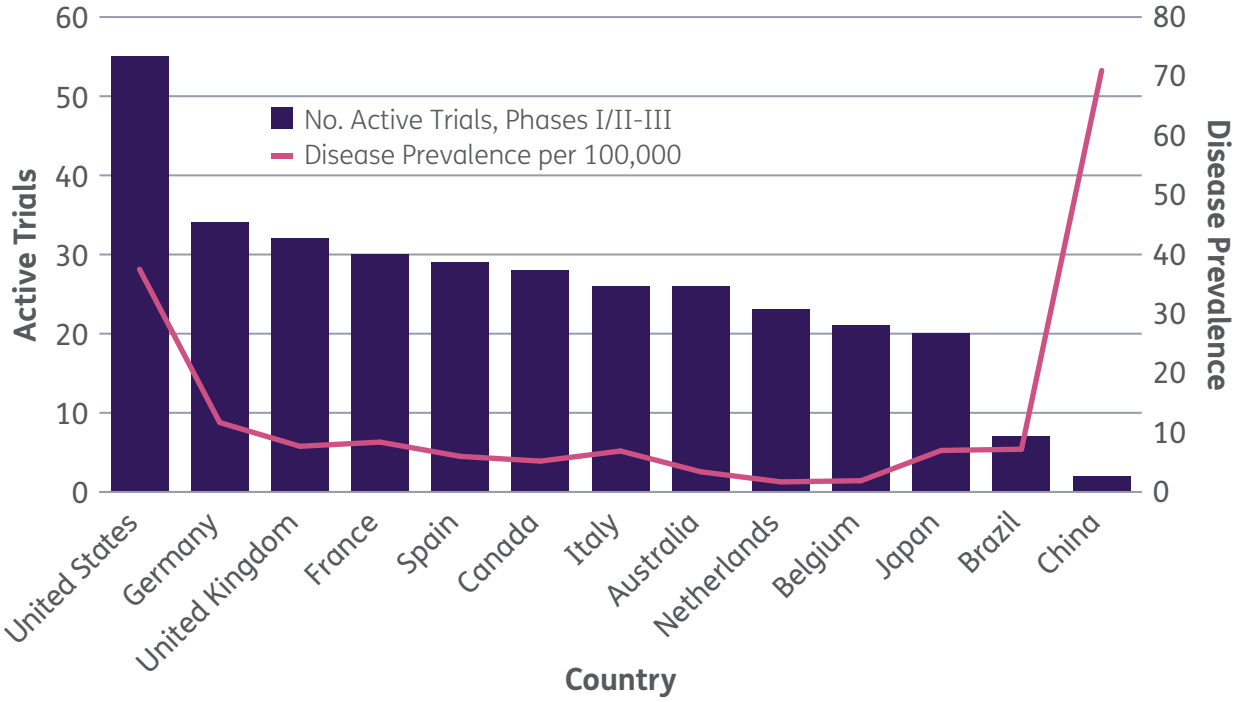
Figure 5: Top Sponsors with ≥ 3 Active Trials for Early Stage Alzheimer's



Source: Trialtrove®, December 2015

Overall, trial activity for early stage Alzheimer's disease is greatest in the 7 major markets (US, UK, Germany, France, Spain, Italy, Japan), while disease prevalence is highest in China, followed by the US. In line with the high prevalence of 375 in 100,000, the US has the greatest number of active Alzheimer's trials (55). On the other hand, China has the lowest number of active trials (2) despite having the highest disease prevalence (64 in 100,000). [Figure 6]

Figure 6: Active Trials for Early Stage Alzheimer's Disease by Location and Disease Prevalence



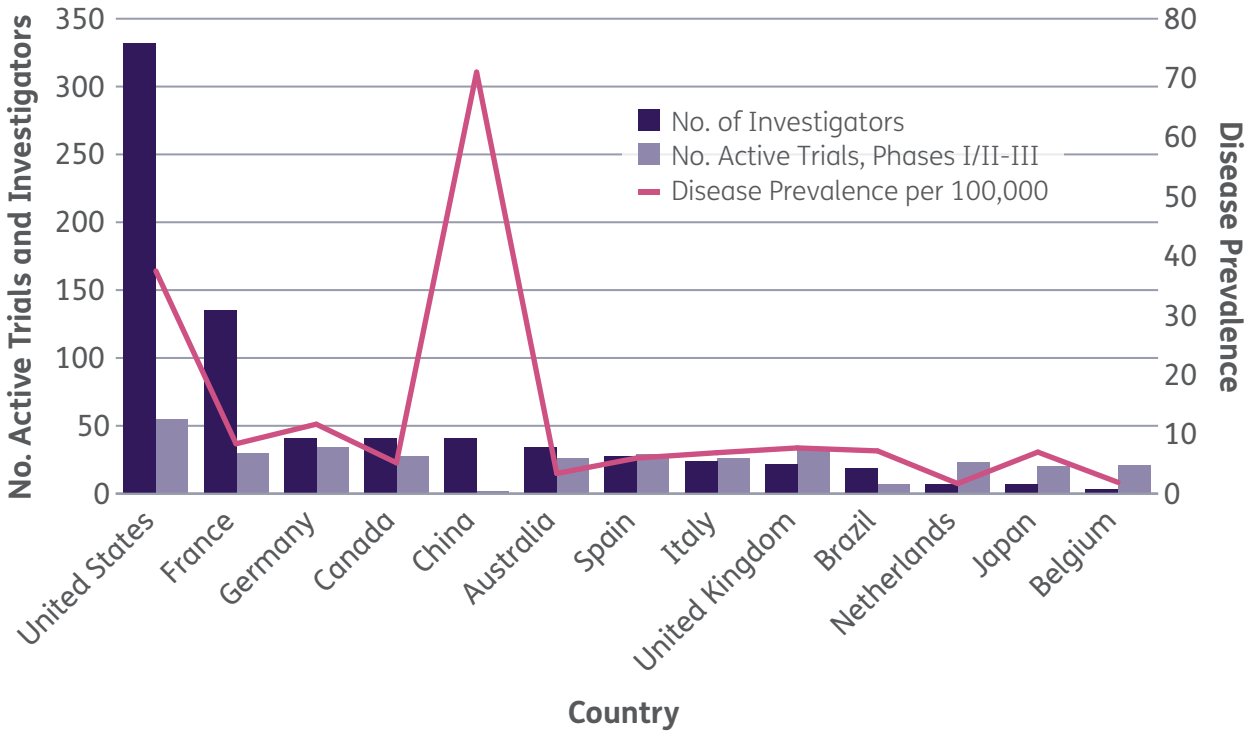
Source: Trialtrove®, Datamonitor Healthcare®, Alzheimer Europe Organization, Alzheimer Society Canada, Alzheimer's Australia, December 2015

Where are the Investigators?

How does the top trial locations for early stage Alzheimer's and disease prevalence compare with the number of top investigators located in these countries? Sitetrove's® Investigator Prioritization functionality was utilized to identify investigators with the greatest experience in early Alzheimer's and the highest

probability to perform well in a trial collectively. This proprietary algorithm incorporates aspects of overall trial experience, availability, recentness of activity, and disease specific search parameters, in order to rank investigators into three tiers. In Sitetrove®, there are 853 Tier 1 and Tier 2 investigators with direct experience in early stage Alzheimer's research, no FDA regulatory actions, and no identified, competing phase I/II-III industry sponsored early Alzheimer's trials. Of these investigators, the majority are located in the United States (332), followed by France (135), then China, Canada, and Germany, each with 41. [Figure 7]

Figure 7: Active Alzheimer's Disease Trials, Disease Prevalence, and Tier 1 & 2 Investigators*



*Tier 1 and 2 investigators have direct experience in early stage Alzheimer's trials, no FDA regulatory actions, and no identified, competing trials.

Source: Trialtrove®, Sitetrove®, Datamonitor Healthcare®, Alzheimer Europe Organization, Alzheimer Society Canada, Alzheimer's Australia, December 2015

Considering the low trial activity, high disease prevalence, and top investigator experience in Brazil and China, it may be worthwhile to consider these countries for future Alzheimer's trials. With that in mind, Chinatrove® shows 138 hospitals with active CFDA certifications in neurology or psychiatry. Each of the 41 top investigators in China, are specialists at a highly qualified hospital (Tier 3A or 3B) with an active neurology or psychiatry certification (Data not shown).

A Deeper Dive: Protocol Driven Elements of Site Selection

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hospitals with active CFDA certifications in neurology or psychiatry.

Other factors to consider in the selection process apart from trial locations, disease prevalence, and top investigators, are protocol specific requirements. With the rise in Alzheimer's disease cases year on year, the need for early detection is key, and therefore, the use of biomarkers in Alzheimer's trials has increased. The National Institute on Aging and Alzheimer's Association, outlined new guidelines recommending the use of biomarkers in Alzheimer's disease clinical development [9,10]. The role of biomarkers in Alzheimer's trials varies depending on the stage of the disease, however for early stage Alzheimer's, biomarkers can be used to establish the disease presence in patients with very subtle or no symptoms[11].

Cerebrospinal fluid (CSF) assessment is used to identify the levels of two key proteins, beta amyloid and tau, found in the brains of Alzheimer's disease patients. The levels of the two proteins in the cerebrospinal fluid makes up the neurochemical biomarkers most frequently evaluated in clinical trials[9]. According to Trialtrove®, the percentage of active early Alzheimer's trials involving CSF

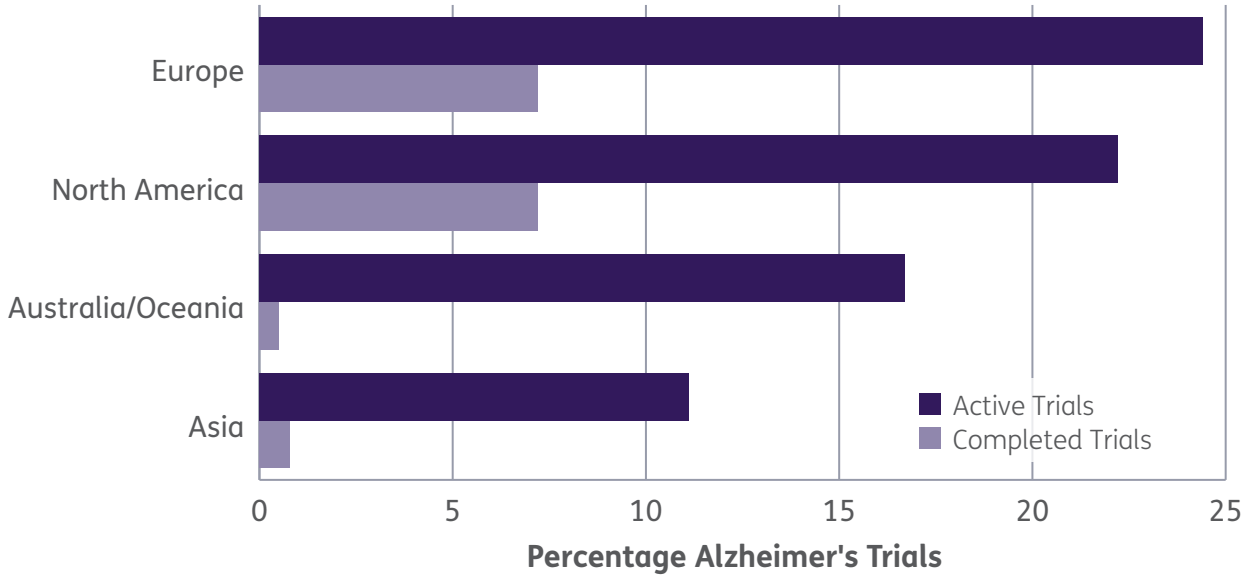
[9] *Citeline: https://citeline.com/biomarkers-alzheimers-trials-longest-day/*

[10] *McKhann G. et al. (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines*

[11] *Alzheimer's Association: http://www.alz.org/documents_custom/intro_diagnostic_recommendations_alz_proof.pdf for Alzheimer's disease. Alzheimers Dement. May 2011; 7(3): 263–269.*

assessment has increased across all regions when compared to previously completed trials. Experience appears to be concentrated in Europe and North America since both countries maintain the greatest percentage of early stage Alzheimer's trials involving CSF assessment. [Figure 8]

Figure 8: Early Stage Industry-Sponsored Alzheimer's Trials Involving Cerebrospinal Fluid (CSF) Assessment by Region and Trial Status



Source: Trialtrove®, December 2015

However, even with the increasing volume of trials involving this procedure (or other invasive procedures), there has been a trend toward declining recruitment rates for Alzheimer's trials with biomarkers. Benchmarking recruitment rates ahead of time can help determine how many sites may be needed to attain target enrollment rates. Given this potential trend, a larger number of sites may be needed for early stage Alzheimer's trials using biomarkers. [Figure 9]

Figure 9. Enrollment Rates for Trials with and without a Biomarker (CSF, Imaging/PET, or Other)[12]

	"Median Patients/Site/Month"	
Time Period	**Biomarker (+)**	**Biomarker (-)**
2008-2010	0.60	0.51
2011-2013	0.49	0.78

Source: Trialtrove® and Trialpredict®, January 2016

Other factors to bear in mind while selecting countries for active comparator studies are the treatment guidelines and standard of care. It is important to identify countries where active drugs or baseline medications required for the study protocol are launched and widely prescribed. Country-specific prescribing trends, including the distribution of approved drugs that the patient population is receiving, can facilitate identification of potential countries. For instance, the US should be considered for trials using donepezil as an active comparator, or France for rivastigimine. [Figure 10]

[12] *Enrollment rate of "patients/site/month" is a calculation based on trial-level metrics and does not represent actual site metrics.*

Figure 10. Country-Specific Prescribing Trends for the US and France


	United States	France
Pharmacological treatment only	40.9%	39.8%
Pharmacological and non-pharmacological treatment	42.7%	37.6%
Non-pharmacological treatment only	8.6%	9.9%
Not currently receiving treatment	7.8%	12.7%
Donepezil	36.7%	24.7%
Galantamine	11.8%	12.4%
Oral rivastigmine	3.4%	6.6%
Transdermal rivastigmine	14.9%	39.9%
Memantine	9.6%	10.7%
Donepezil plus memantine	13.9%	0.8%
Galantamine plus memantine	3.1%	0.8%
Oral rivastigmine plus memantine	1.6%	0.6%
Transderm rivastigmine plus memantine	5.0%	3.1%
Other	0.2%	0.2%

Source: Datamonitor Healthcare®, Januray 2016

Conclusion

Alzheimer's disease is a global epidemic affecting millions. As the Alzheimer's population and market continue to expand globally, it is critical that Alzheimer's research is fast-tracked. Data driven approaches to country, site, and investigator selection can guarantee the best-informed decisions are made, and integrating multiple data sources using the highest quality data available, ensures the greatest potential for recruitment success in your next Alzheimer's trial.