# Disease State Primer: Alzheimer's Disease

Q4 2011 Update

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Lumleian offers the requisite scale and depth of life science expertise required for our client's most critical investment decisions; We offer universal information and real time knowledge.

## Expertise Based Teams

- Experience
  - Academic faculty
  - Bio-pharmaceutical
  - Equity research
  - Strategy consulting
- Expertise
  - 30+ clinicians and Ph.D. scientists
- Analytics
  - 5 Ph.D. economists and statisticians

## Universal Information

- Data Mining
  - Regulatory filings
  - Scientific literature
  - Patent filings
  - Company filings and press releases
- Secondary Data
  - Industry pipelines
  - Wall Street analysis
  - US TRx, pricing, promotional spend
- Primary Research
  - Key opinion leaders
  - Practicing physicians
  - Reimbursement

## Real-Time Knowledge

- Disease State Primers
  - Disease overview and care paradigm
  - Clinical development pipeline
  - Commercial landscape
- Functional Drill Downs
  - In licensing assessments
  - Early and late stage
  - Preliminary due dilligence
  - Real-time clinical data
- Proprietary Analytics
  - Asset valuation
  - Epidemiologic forecasts
  - Industry benchmarks
    - Drug Development and commercial
  - Patient segment valuations
  - Promotional response models
    - Healthcare professional and direct to consumer

## Decision Support

## Life Science Client Base

- Academic and Research Institutions
  - Portfolio optimization
    - Early stage
  - Out licensing strategy
    - Asset valuation
    - Transaction support
    - Royalty monetization
- Bio-pharmaceutical Companies
  - Asset valuation
  - Clinical strategy
  - In licensing strategy
    - Early and late stage
  - Portfolio optimization
    - Early and late stage
  - Preliminary due dilligence
- Life Science Investors
  - Asset valuation
  - Clinical strategy
  - In licensing strategy



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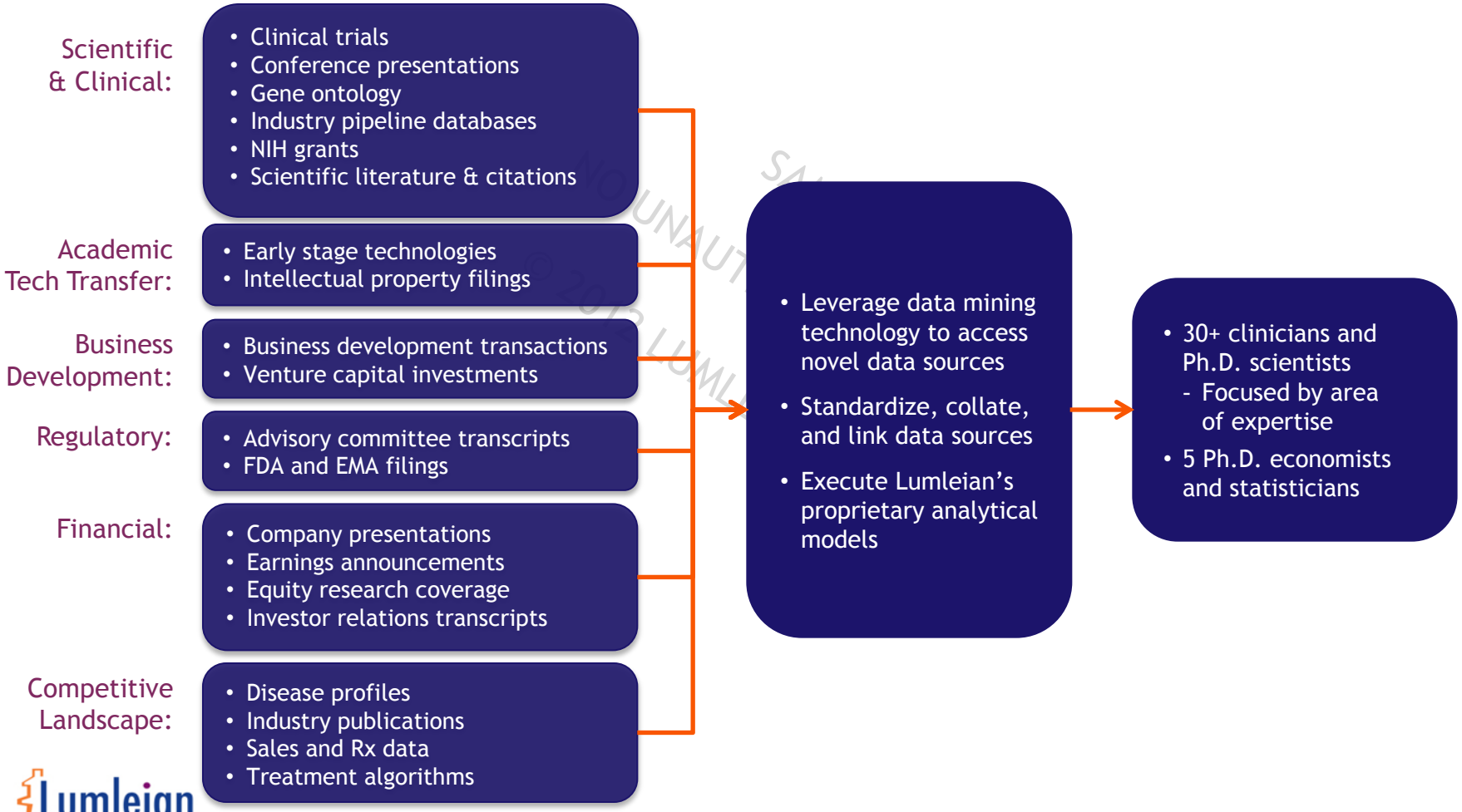
To ensure real-time knowledge, across disease states, our team of 30+ clinicians and Ph.D. scientists maintain a comprehensive knowledge management platform, leveraging novel data mining technology and proprietary analytics.

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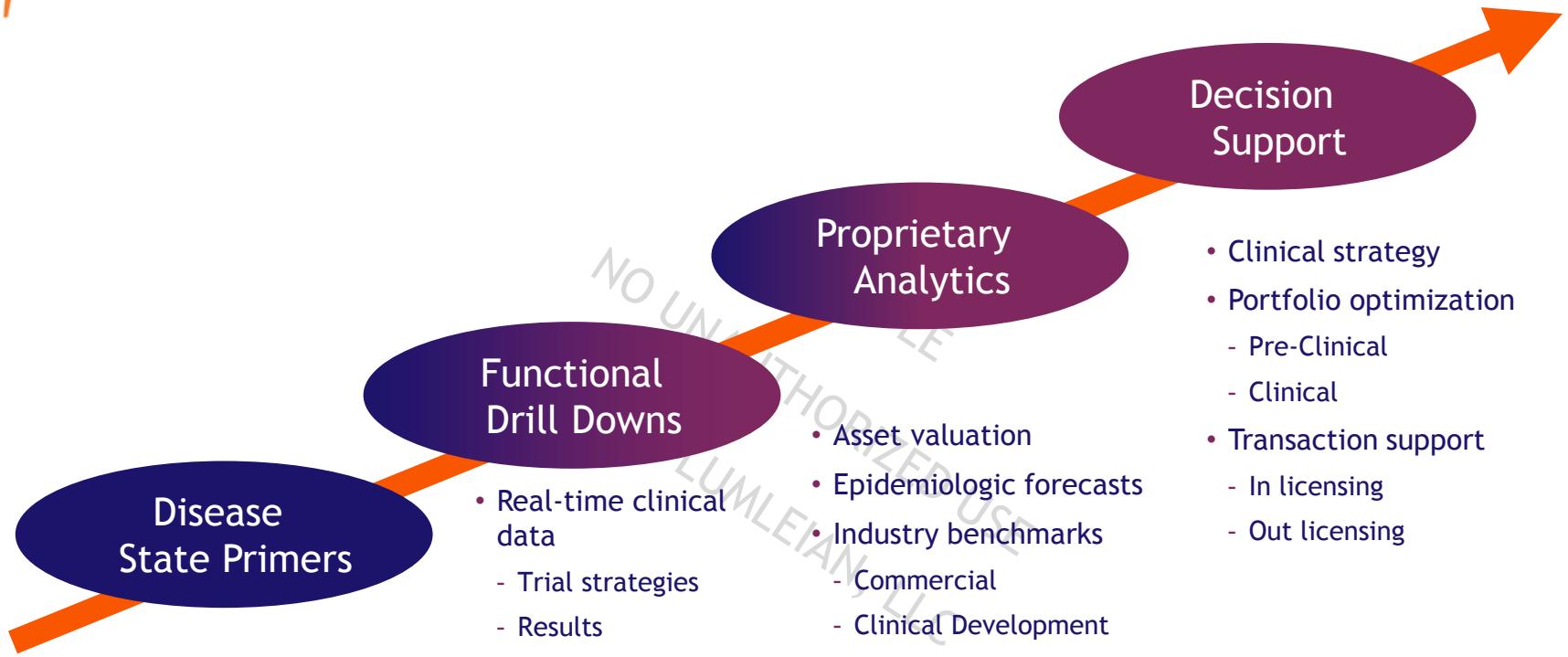
Notes: [1]These are a representative sub-set of the publicly available data sources

Our efficient platform and our expertise based teams enable us to both deliver the highest quality product and tailor our offer, to specific client needs: Either custom decision support or more standardized research and analytics, e.g. disease state primers.




- Disease overview and care paradigm
- Clinical development pipeline
- Commercial landscape

- Real-time clinical data
  - Trial strategies
  - Results
- In licensing assessments
  - Pre-clinical
  - Clinical
- Preliminary due dilligence
  - Scientific
  - Clinical
  - Commercial

- Asset valuation
- Epidemiologic forecasts
- Industry benchmarks
  - Commercial
  - Clinical Development
- Patient segment valuations
- Promotional response models
  - Healthcare professional
  - Direct to consumer
- Royalty monetization

- Clinical strategy
- Portfolio optimization
  - Pre-Clinical
  - Clinical
- Transaction support
  - In licensing
  - Out licensing

Customized

Standardized



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# What is a Lumleian's disease state primer?

## What information is included in a disease state primer?

- Lumleian's objective and fact based perspective on the relative attractiveness of investing in a given disease state
- Disease overview and care paradigm
  - Etiology, Diagnosis and patient segmentation, Global epidemiology, Treatment algorithm, Clinical evidence, Emerging care paradigm
- Clinical Development Pipeline
  - Validated industry pipeline for all assets in clinical development, Select mechanism of action profiles, trial designs and evidence
- Commercial landscape
  - Global, US, EU, Japan market and brand revenue, Pipeline forecasts, US growth decomposition, Promotional spend and messaging

## What disease states are planned for 2012?

- Autoimmune: Inflammatory Bowel Disease, Lupus, Multiple Sclerosis, Psoriasis, Rheumatoid Arthritis
- Cardiovascular: Hyperlipidemia
- Central Nervous System: Alzheimer's Disease, Depression, Pain, Schizophrenia
- Endocrine: Type II Diabetes, Obesity
- Infectious Disease: Gram Negative Bacteria, Hepatitis C Virus
- Oncology: Breast, Colorectal, Leukemia(s), Lung, Lymphoma(s), Melanoma, Ovarian, Pancreatic, Prostate
- Pulmonary: Chronic Obstructive Pulmonary Disease, Idiopathic Pulmonary Fibrosis

## Are disease state primers real-time, based on the latest validated scientific, clinical, and commercial data?

- Quarterly primers are validated by our team: 30+ clinicians and Ph.D. scientists, 5 Ph.D. economists and statisticians
- Primers are available at the end of quarter, incorporating new commercial and clinical data from the previous quarter
  - Particulary dynaimc disease states are updated around key medical conferences, e.g. HCV post EASL in April and post AASLD in November

## Do we create specific disease state primers and provide more in-depth functional information?

- Yes, we plan to add disease states throughout '12, per client interest
- Yes, we are developing deep drills by function, e.g. Discovery, Clinical development, Business development, Commercial

## Why did we create our disease state primers?

- We were frustrated by having to repeatedly validate, standardize, and collate pipeline and commercial data
- Portfolio optimization requires a standard framework to compare "apples to apples" investment decisions across disease states
- Our primers began as a training tool; We require every decision scientist create one from scratch before supporting clients



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# Executive Summary: Alzheimer's Disease

| | |
|---|---|
| Disease Overview and Care Paradigm | • AD is a devastating, age-related, neurodegenerative disorder characterized by progressive cognitive, functional, and behavioral impairment<br>• Under the current standard of care, AChE Inhibitors are used to slow the rate of progression with NMDA antagonists added as the disease progresses; This provides symptomatic relief and temporarily improves cognitive function for 6-12 months; Prognosis is poor<br>• Looking forward Lumleian foresees step-wise improvement in the care paradigm, including: (1) Genetic testing and diagnostic monitoring, (2) Preventative therapy and use of multi MoA treatment cocktails, (3) Use of bio-markers to monitor progression and inform treatment. |
| Clinical Development Pipeline | • As of Q4, Lumleian validated 69 assets in 'active' clinical development for AD; Beta amyloid targeting strategies dominate the industry's clinical development pipeline<br>- Passive immunotherapies (Monoclonal antibodies and Intravenous immunoglobulins), Active immunotherapies, Aggregation inhibitors, Neuronal restorers, Gamma secretase inhibitors, and Beta secretase Inhibitors<br>• Bapineuzumab's phase II data was impressive in the ApoE4 (-) cohort: Achieved SSI in 3 of 4 efficacy end points without an increased risk for vasogenic edema; Bapineuzumab's ph. III trial prospectively stratifies by ApoE4<br>• Solanezumab's interim phase II data suggests an attractive safety profile (vs. Bapineuzumab) and pharmacodynamic effect (CSF and plasma biomarkers); Efficacy and dose response data is indeterminate; Phase III trials are not prospectively stratified by ApoE4 status<br>• Phase I data from Gantenerumab, which targets both the mid domain and N-terminus, indicated strong dose response and rapid amyloid reduction; Vasogenic edema was a concern at a high dose and in ApoE4 homozygotes, similar to Bapineuzumab<br>• Gammagard, albeit in an small phase II study, showed SSI, in both cognition and function, as well as lower brain ventricular enlargement rates; Baxter is funding a single phase III study which began enrolling in the second half of '10<br>• Avagacestat is tolerable in lower doses (25 mg, 50mg) but higher doses (100 mg, 125 mg) had ~40% discontinuation rates due to GI and dermatological side effects |
| Commercial Landscape | • Global '11 brand revenue fell 22.6% to ~$5.7B versus '10, driven by US generic donepezil penetration; The market is forecast to plateau through '15, with the anticipated launches of the first anti beta amyloid monoclonal antibodies offsetting generic penetration<br>• Wall Street consensus estimates forecast new product launches will increase the '15 global market by ~$700M, driven largely by anticipated launches for Pfizer/JNJ/Elan's Bapineuzumab and Eli Lilly's Solanezumab |

The global



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# What are the key questions for 2012?

## Key Questions

- Solanezumab: The two phase III trials (Expedition 1 and 2), are enrolling a mix of ApoE4 carriers and non-carriers, presumably in proportion to ApoE4 status in trial geographies:
  - If efficacy is related to ApoE4 status, will the signal in ApoE4 non-carriers be sufficiently strong in a pooled population?
  - If a signal is observed in ApoE4 non-carriers, but not in ApoE4 carriers, given the high level of unmet need, how will regulatory agencies treat results from a post-hoc stratification?
  - If an additional phase III trial is required in ApoE4 non-carriers, will Lilly pursue the requisite investment, conditional on the results of Expedition 1 and 2? How long would it take to design, enroll, and execute?
- Bapineuzumab: Data from the US phase III trials (ApoE4 carriers and non-carriers) reads-out in '12
  - If a signal is observed in ApoE4 non-carriers, but not in ApoE4 carriers, will regulatory agencies require supporting data from the Global ApoE4 non-carrier study for approval?
  - If a signal is observed in both US studies (ApoE4 carriers and non-carriers), how will regulators treat vasogenic edema, if it is a concern in ApoE4 carriers?

## Lumleian's Perspective

- Monoclonal Antibodies: Drawing inferences from the available clinical data, suggests that:
  - Monoclonal antibodies are more likely to be efficacious in ApoE4 non-carriers, per Bapineuzumab's phase II data
  - Treatment differences are likely to emerge in year one, as suggested by both Bapineuzumab and Gantenerumab
  - Vasogenic edema is more likely to be a concern in ApoE4 carriers (heterozygotes), and more-so in homozygotes as evidenced by Bapineuzumab's phase II data and Gantenerumab's phase I data
    - Vasogenic edema is likely related to clearance from the brain (recognition of B-cell epitopes in the N-terminus of the beta amyloid peptide), as it has not been observed in patients treated with Solanezumab
  - It is estimated that ~60% of Northern European and North American's are ApoE4 carriers
- Gamma Secretase Inhibitors: Toxicity will likely remain a concern for pipeline agents, given withdrawal of Semagacestat and high discontinuations rates at higher doses of Avagacestat



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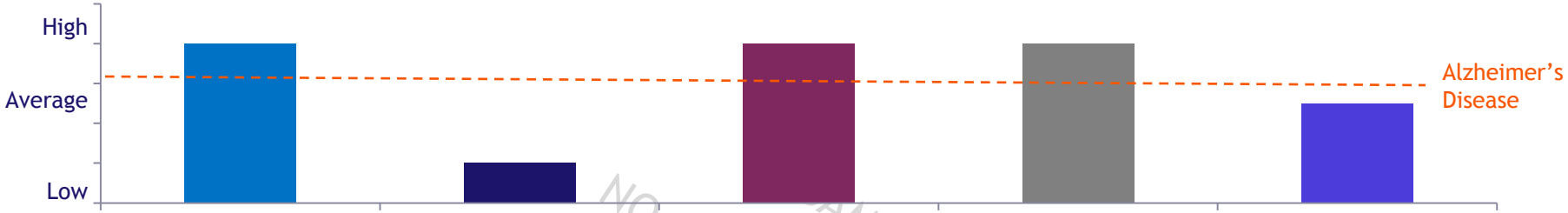
# Greenfield investment in late stage clinical development, for Alzheimer's disease is a high risk vs. high reward proposition; The likelihood of technical success is relatively low but the levels of unmet need, the regulatory environment, and the commercial landscape are relatively attractive.

## Alzheimer's Disease: Relative Attractiveness of Greenfield Investment in Late Stage Clinical Development






### Level of Unmet Need

**Clinical Unmet Need**
- High, available agents are symptomatic and temporarily improve cognitive function for 6-12 months

**Global Epidemiology**
- ~35.6 M prevalence '10
- ~3.1% CAGR '10-'15

**Disease Burden**
- Economic cost of $80-$100B annually (US)
- Caregiver burden
- Institutionalization
- Elderly population

**Not a Cause of Mortality**
- Mean life expectancy is ~8 yrs. post diagnosis

### Likelihood of Technical Success

**Poorly Understood Etiology**
- Amyloid hypothesis?
- Role of Tau?

**Historic Ph. III /IIIB Failures**
- Avandia (GSK)
- Dimebon (PFE/MDVN)
- Flurizam (MYGN)
- Lipitor (PFE)
- Semagacestat (LLY)
- Zocor (MRK)
- AZD3480 (AZ/TRGT)

**Statistical Challenges**
- Subjective outcome measures
- Placebo efficacy curves

**Target Patient Populations**
- Emerging signal (e.g. ApoE4 non-carries), but not clinically confirmed

### Regulatory Environment

**Clinical Unmet Need**
- High, available agents are symptomatic and temporarily improve cognitive function for 6-12 months

**Historical Precedents**
- In July '11 the FDA eased cerebral microhemmorhage guidelines
- In April '11 Aricept's weekly transdermal received complete response
- In June '10 Namenda XR approved
- In '03, Namenda NDA approved 1st cycle (10 months)

**Advocacy**
- Alzheimer's Association

### Commercial Attractiveness

**Market Size**
- ~$5.7B market in '11

**Chronic Condition**
- Mean life expectancy is ~8 yrs. Post diagnosis

**Global Epidemiology**
- ~35.6 M prevalence '10
- ~3.1% CAGR '10-'15

**Market Expansion**
- Prodromal AD and earlier diagnosis

**Generic Penetration**
- ~55% in US '11
- US/EU LoEs through '15
  - Exelon transdermal
  - Namenda IR

**Competitive Launches**
- 5 Ph. III /US reg. assets

**Payor (Rx)**
- Primarily 3rd party

### Required Investment

**Phase III Investment**
- ~2,000 patients in 2 trials
- 18 months duration
- PET scans

**Commercial Spend**
- In Oct '11 the average brand spent ~$5.6M a month on promotion
  - Healthcare professional
  - Direct to consumer

**Phase IV Investment**
- Historically not a substantial investment
- Going forward prodromal AD is a likely investment
  - Gantenerumab
  - Avagacestat

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# Executive Summary: Disease Overview and Care Paradigm

| | |
|---|---|
| What is Alzheimer's disease? | • AD is a devastating, age related, neurodegenerative disorder characterized by progressive cognitive, functional, and behavioral impairment<br>- AD is the most common cause of dementia (60-70% of total)<br>• The amyloid hypothesis has emerged, not without questions, as the consensus causative explanation for AD<br>- Aging and genetics (ApoE4 carrier status) are primary risk factors |
| What is the disease burden? | • Global Alzheimer's disease prevalence was ~36M in '10, with an incidence of ~6M<br>- Prevalence is forecast to grow by ~3.1% to ~56M in '25<br>- US '10 prevalence was ~5M, with incidence of ~600K<br>• AD is not a cause of mortality, mean life expectancy is ~8 yrs. post diagnosis<br>• AD is a significant public health problem, and costs $80-100B annually the US |
| What is today's care paradigm? | • Today patients are screened, classified and monitored based on cognitive impairment using MMSE score<br>- Prodromal AD, a pre-dementia where symptoms are present but do not impact activities of daily living, is not currently diagnosed or treated<br>• Under the current standard of care, AChE Inhibitors are used to slow the rate of progression with NMDA antagonists added as the disease progresses; This provides symptomatic relief and temporarily improves cognitive function for 6-12 months; Prognosis is poor<br>- Aricept is the SoC for mild/moderate patients based on its QD dosing and side-effect profile; A high dose is indicated for moderate/severe; Exelon, for mild/moderate patients, is dosed BID but has GI related side effects; A transdermal formulation offers an improved GI profile<br>- Namenda is approved for moderate/serve patients and is currently available BID; Launch of an approved QD formulation is anticipated for late '12 or early '13; The majority, >60%, of usage is combined with an an AChE inhibitor based on phase III data and a benign AE profile |
| What is the emerging care paradigm? | • Looking forward Lumleian foresees step-wise improvement in the care paradigm, including:<br>- Genetic testing and diagnostic monitoring<br>- Preventative therapy and use of multi MoA treatment cocktails<br>- Use of bio-markers to monitor progression and inform treatment |



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# What is Alzheimer's Disease?

| | |
|---|---|
| Description | • AD is a devastating, age-related, neurodegenerative disorder characterized by progressive cognitive, functional, and behavioral impairment<br>- AD is the most common cause of dementia (60-70% of total)<br>- Common co-morbidities include: Cardiovascular disease (~33%), sensorial handicap (~25%), neurological diseases (~20%) |
| Etiology | • The amyloid hypothesis, not without questions, has emerged as the consensus causative explanation for AD<br>- Genetic linkages exist via ApoE mediated facilitation of beta amyloid degradation<br>- In vitro studies show ApoE4 also increases phosphorylation of tau<br>• Aging and genetics (ApoE4 carrier status) are primary risk factors<br>- Educational status, gender, and race are secondary risk factors |
| Symptom Progression | • Cognitive deficits include memory loss, language dysfunction, visuospatial skills<br>• Functional impairment impedes activities of daily living, with occupational and social consequences<br>• Behavioral symptoms include depression, anxiety, agitation, aggression, and psychosis |
| Disease Burden | • AD is not a cause of mortality, mean life expectancy is ~8 yrs. post diagnosis<br>• AD is significant public health problem, and costs $80-100B annually the US<br>- The majority of severe patients are institutionalization due to functional impairment or behavioral symptoms<br>- Costs are largely borne by caregivers who either pay for institutional care or forego earnings to care for patients at home |

1. Is AD's etiology well understood?

| | |
|---|---|
| Yes | No |

2. Is AD a primary cause of mortality?

| | |
|---|---|
| Yes | No |

3. Is AD an acute or chronic disease?

| | |
|---|---|
| Acute | Chronic |

4. Is AD a communicable disease?

| | |
|---|---|
| Yes | No |

5. What is AD' s treatment goal?

| | | |
|---|---|---|
| Symptom Relief | Disease Treatment | Disease Cure |

6. Which specialties treat AD, commonly?

| | | |
|---|---|---|
| PCP | Neurology | Psychiatry |

7. Where is AD treated, commonly?

| | | |
|---|---|---|
| Out Patient | Inpatient Hospital | Long Term Care |

8. Who pays for AD care (Rx), commonly?

| | | |
|---|---|---|
| 3rd party | Cash | Medicaid |

9. Does AD impact a special populations?

| | |
|---|---|
| Yes: Elderly | No |



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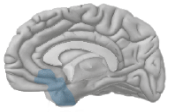
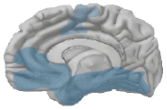
Sources: Alzheimer's Association; Aratz, M.A. et al. Medical comorbidity in Alzheimer's disease: baseline characteristics of the REAL.FR Cohort. Rev Med Interne. 27(2), 91-97 (2006) ; Doraiswamy, P.M. et al. Prevalence and impact of medical comorbidity in Alzheimer's disease. J Gerontol A Biol Sci Med Sci. 57(3), 173-177 (2002)

Today patients are screened, classified and monitored based on cognitive impairment using MMSE score; Prodromal AD, a pre-dementia where symptoms are present but do not impact activities of daily living, is not currently diagnosed or treated.

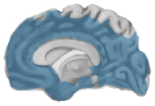
Prodromal AD



- Plaques develop in Enthorial cortex



- Plaques spread to the Hippocampus



- Plaques reach the Neocortex

| | | | Mild (2-4 years) | Moderate (2-10 years) | Severe (1-3 years) |
|---|---|---|---|---|---|
| Diagnosis | Criteria | MMSE score | • 21-25 | • 10-20 | • < 10 |
| | Presenting Symptoms | Cognition | • Mild memory loss | • Impaired judgment | • Severe cognitive decline |
| | | Behavior | • Apathy and depression | • Increased aggression | • Severe |
| | | Function | • Remain functional<br>• Independent | • Difficulty working, driving, and performing activities of daily living<br>• Increasingly dependent | • Difficulty walking, swallowing, and speaking<br>• Requires 24 hour care |
| Treatment | 1st line | Initiate | • AChE Inhibitor (Aricept)<br>- Mono-therapy | • AChE Inhibitor (Aricept)<br>- Mono-therapy | • AChE Inhibitor (Aricept) and NMDA antagonist (Namenda)<br>- Combination therapy |
| | 2nd line | Switch | • AChE Inhibitor (Exelon) | • AChE Inhibitor (Exelon) | |
| | | Add | • NMDA antagonist (Namenda) | • NMDA antagonist (Namenda) | |
| | PRN | | • Antidepressant | • Antidepressant<br>• Antipsychotic<br>• Anticonvulsant | • Antidepressant<br>• Antipsychotics<br>• Anticonvulsant |



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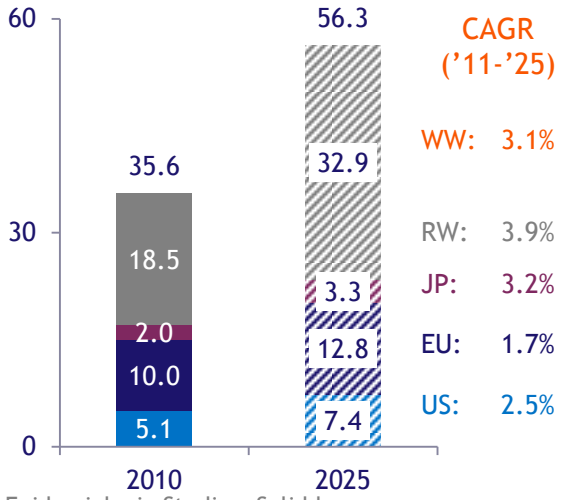
Sources: American Psychiatric Association. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias. (2007)

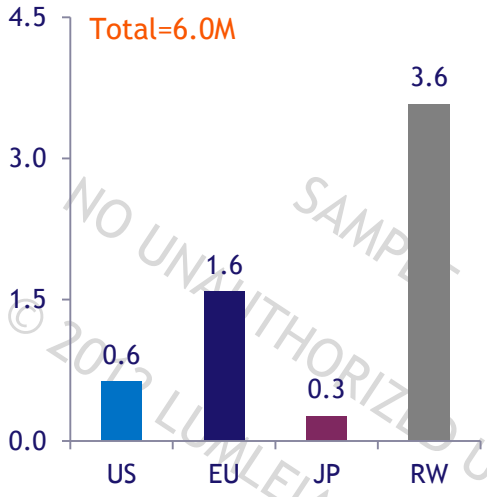
# Global AD prevalence was ~36M in '10, with an incidence of ~6M; Prevalence is forecast to grow by ~3.1% to ~56M in '25; US '10 prevalence was ~5M in '10, with incidence of ~600K; Age and genetics (ApoE4 carrier status) are primary risk factors.

AD Global Prevalence (M)

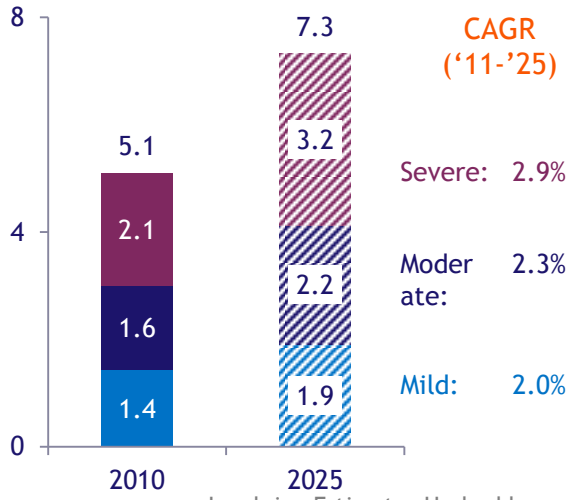



Epidemiologic Studies: Solid bars

2010 AD Global Incidence (M)




AD US Prevalence by Patient Segment (M)




Lumleian Estimate: Hashed bars



## Primary Risk Factors

- Age: Aging is the dominant risk factor and the risk doubles every 5 years after the age of 65
- Genetics: ApoE4 carrier status is a primary risk factor impacting outcomes; ApoE4 carriers (homozygotes) are at 15 fold higher risk and (heterozygotes) are at 3 fold higher risk
  - In phase II trials, Bapineuzumab slowed progression in ApoE non-carriers but not in carriers
  - is estimated that ~60% of Northern European and North American's are ApoE4 carriers

## Secondary Risk Factors

- Gender: Women are at higher risk than men, which is largely explained by differences in life expectancy
- Educational: People with fewer years of education are at higher risk, but this has not been found to be SS
- Race: African Americans are at 1.5 fold higher risk than Caucasians, but this has not been found to be SS

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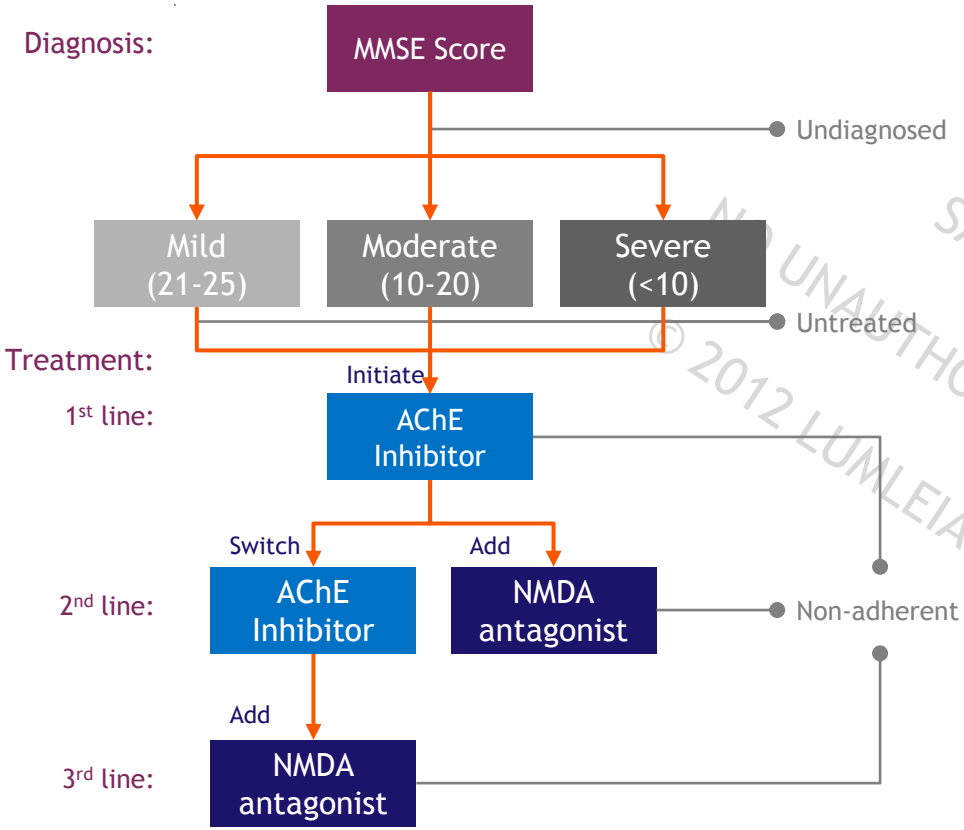
Notes: Global incidence and prevalence estimates exclude the prodromal AD segment

Sources: Ferri, C.P. et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 366, 2112-2117 (2005); Plassman, B.L. et al. Prevalence of dementia in the United States: The Aging, Demographics, and Memory Study. Neuroepidemiology. 29(1-2), 123-132 (2007); Alzheimer's Association. Changing the Trajectory of Alzheimer's Disease: A National Imperative. (2009)

# Under the current standard of care, AChE Inhibitors are used to slow the rate of progression with NMDA antagonists added as the disease progresses; This provides symptomatic relief and temporarily improves cognitive function for 6-12 months; Prognosis is poor.




## Diagnosis (Current)

- Diagnosis is based on medical history, mental status testing and exams, both physical and neurological
- Blood tests and brain imaging are used to rule out other causes of dementia-like symptoms, e.g. blood sample analysis, MRI, and CT scans

## Treatment (Current)

- Existing treatments provide symptomatic relief and temporarily improving cognitive function
- AChE inhibitors preserve cell to cell communication and brain function, for 6-12 months, but do not halt neuronal death
  - Aricept (Donepezil), indicated for mild-severe patients, is the SoC based on its QD dosing and side-effect profile
    - A high dose tablet is indicated for moderate/severe patients
  - Exelon (Rivastigmine), indicated for mild/moderate patients, is dosed BID dosing and has GI related side effects
    - A transdermal formulation offers an improved GI profile.
- NMDA antagonists block sustained, low level activation, of the NMDA receptor, resulting from increased glutamate activity, and do not inhibit normal function in memory and cognition
  - Namenda (Memantine) is approved for the treatment of moderate to serve AD, but not for mild to moderate AD, off-label use is common
    - Initially used BID, a QD formulation was approved in 07/10
- The majority, 60%, of Namenda's usage is in combination with an an AChE inhibitor

## Prognosis (Current)

- Mean life expectancy after diagnosis is ~8 years, under the current care paradigm



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Sources: American Psychiatric Association. Practice guideline for the treatment of patients with Alzheimer's disease and other. (2007)

# Aricept is the SoC for mild/moderate patients based on its QD dosing and side-effect profile; A high dose is indicated for moderate/severe; Exelon, for mild/moderate patients, is dosed BID but has GI related side effects; A transdermal formulation offers an improved GI profile.

| | Aricept (Donepezil Hydrochloride) | Exelon (Rivastigmine Tartrate) |
|---|---|---|
| MoA | • AChE inhibitor | • AChE inhibitor |
| Sponsor | • Pfizer/Eisai | • Novartis |
| Formulation (Generic) | • Tablet (5 mg, 10 mg); ODT (5 mg, 10 mg)<br>- Available as generic<br>• Tablet (23 mg) | • Tablet (1.5 mg, 3 mg, 4.5 mg, 6 mg); Oral solution<br>- Available as generic<br>• Transdermal (9 mg, 18 mg) |
| Dosing | • Tablet: QD | • Tablet: BID<br>• Transdermal: 24 hours |
| Indications | • Mild to Moderate Alzheimer's disease<br>- 5 mg and 10 mg had SSI vs. placebo on ADAS-cog and on CIBIC+ function after 24 weeks (N=473)<br>• Moderate to Severe Alzheimer's disease<br>- 10 mg had statistically significant improvement vs. placebo on SIB cognition and ADCS-AD function after 6 months (N=248)<br>- 23 mg had SSI vs. 10 mg formulation on SIB cognition, but not on the CIBIC+ function after 24 weeks (N=1,434) | • Mild to Moderate Alzheimer's disease<br>- 1-4 mg or 6-12 mg had SSI vs. placebo on ADAS-cog and CIBIC+ function after 26 weeks (N=699)<br>- 6-12 mg had SSI vs. placebo on ADAS cognition and CIBIC+ function after 26 weeks, but 1-4 mg did not on either endpoint (N=725)<br>- 6 or 9 mg/day fixed dose had SSI vs. placebo on ADAS-cog but not on CIBIC+ and 3mg not on either end point (N=702)<br>- Transdermal vs.6mg BID vs. placebo had SSI on ADAS cognition and ADCS-CGIC function after 24 weeks (N=1,195) |
| Adverse Events (Discontinuations) | • Tablet: Nausea (1-3%), Vomiting (1-2%) | • Tablet: Nausea (8%), Vomiting (5%)<br>• Transdermal: Vomiting (0%) |
| Lumleian Commentary | • In 04/11 the FDA issued a complete response letter for Aricept's weekly transdermal formulation | • Exelon is not approved for use in moderate to severe patients |

Notes: Exelon is also approved for Mild to moderate Parkinson's disease; Adverse events are reported discontinuation rates from phase III trials

Sources: Aricept and Exelon prescribing information; Company press releases

Namenda is approved for moderate/serve patients and is currently available BID; Launch of an approved QD formulation is anticipated for late '12 or early '13; The majority, >60%, of usage is combined with an an AChE inhibitor based on phase III data and benign AE profile.

| | Namenda (Memantine Hydrochloride) |
|---|---|
| MoA | • NMDA activator |
| Sponsor | • Forest Laboratories / Merz Pharmaceuticals |
| Formulation (Generic) | • Tablet (5 mg, 10 mg); Oral solution<br>• Extended Release Tablet (28 mg) |
| Dosing | • Tablet: BID<br>• Extended Release Tablet: QD |
| Indications | • Moderate to Severe Alzheimer's disease<br>- 10 mg BID (post titration) had statistically SSI vs. placebo on SIB cognition and ADCS-ADL function after 28 weeks (N=252)<br>- 10 mg BID (post titration) in combination with Aricept had SSI vs. placebo on SIB cognition and ADCS-ADL function after 24 weeks (N=404)<br>- 28 mg QD in combination with an AChE inhibitor had SSI vs. placebo on SIB cognition and CIBIC+ function after 24 weeks (N=677) |
| Adverse Events (Discontinuations) | • The likelihood of AE discontinuation was equivalent in the Namenda and placebo arms<br>- No AE was associated with discontinuation of treatment in 1% (or greater) of Namenda treated patients |
| Lumleian Commentary | • In 06/10 the FDA approved Namenda's QD formulation (28 mg extended release)<br>• In their Q2 '11 earnings call Forest management signaled XR's launch in late '12 or early '13 based on continued review of patents, with the IR formulation due to loose exclusivity in '15 |



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Notes: Adverse events are reported discontinuation rates from phase III trials

Sources: Namenda prescribing information; Company press releases

## Looking forward Lumleian foresees step-wise improvement in the care paradigm, including: (1) Genetic testing and diagnostic monitoring, (2) Preventative therapy and use of multi MoA treatment cocktails, (3) Use of bio-markers to monitor progression and inform treatment.

### Future Diagnosis

- Imaging technology
  - Eli Lilly / Avid's 18F PET imaging amyloid tracer
  - GE's PiB (Fluorescent thioflavin S)
  - Siemen's PET ligand, which binds to both amyloid plaques and NFTs
- Gene Expression/Profiling
  - Athena's ApoE genotype analysis
  - ExonHit's blood based gene signature assay (EHT Dx21
- Fluid Analytes
  - Athena's CSF measurements of beta-amyloid peptides, t-tau, and p-tau
  - Applied Neurosolution's CSF measurements of p-tau
  - Nymox's urine analysis of neural thread protein levels

### Future Treatment

- Prodromal treatment with an oral small molecule disease modifying agent
  - Gamma secretase inhibitor, e.g. Avagacestat (BMS), BMS708163 (BMS)
  - Aggregation inhibitor, e.g. Scyllo-inositol (ELN)
- Passive or active anti amyloid beta immunotherapy in ApoE4 carriers (Prodromal, Mild/Moderate)
  - Monoclonal antibody, e.g. Bapineuzumab (PFE/JNJ/ELN), Solanezumab (LLY)
  - Intravenous immunoglobulin, e.g. Gammagard (BAX)
  - Active immunotherapy, e.g. ACC-001 (PFE/JNJ/ELN)
- Tau targeting agents aimed at NFTs
  - Aggregation inhibitor, e.g. Rember (TauRx)
  - Phosphorylation Inhibitors, e.g. Nypta (Noscira)
- Symptomatic agents will likely be used in combination with disease-modifying agents to manage behavior
  - AChE inhibitor, e.g. Aricept (Donepezil), Exelon (Rivastigmine)
  - NMDA antagonist, e.g. Namenda (Memantine)

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Sources: Summers, W.K. Current and future treatments of memory complaints and Alzheimer's disease. Therapy. 8(5), 491-504 (2011)

# Table of Contents





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# Executive Summary: Clinical Development Pipeline (1 of 2)

**What is in the industry's clinical development pipeline?**

- The amyloid hypothesis has emerged, not without questions, as the consensus causative explanation for AD
  - Genetic linkages exist via ApoE mediated facilitation of beta-amyloid degradation
- Given a poorly understood etiology, multiple phase III assets have disappointed, e.g.:
  - Avandia (GSK), Dimebon (PFE/MDVN), Flurizam (MYGN), Lipitor (PFE), Semagacestat (LLY), Zocor (MRK)
- Beta amyloid targeting strategies dominate the industry's clinical development pipeline, focused on: inhibiting synthesis, decreasing aggregation, and increasing removal, e.g.:
  - Passive immunotherapies (Monoclonal antibodies and Intravenous immunoglobulins), Active immunotherapies, Aggregation inhibitors, Neuronal restorers, Gamma secretase inhibitors, and Beta secretase Inhibitors
- Tau targeting and Neuronal nicotinic receptor agonists are also being pursued, e.g.:
  - Aggregation inhibitors, Phosphorylation inhibitors, Alpha-4 beta-2 agonists, and Alpha-7agonists
- As of Q4, Lumleian validated 69 assets in 'active' clinical development for AD
  - 5 in US Regulatory/Phase III, 26 in Phase II, and 38 in Phase I

**What is the evidence for late stage assets?**

- Monoclonal Antibodies: Bapineuzumab (PFE/JNJ/ELN) and Solanezumab (LLY), are the most advanced monoclonal antibodies; Bapineuzumab targets the N-terminus and is believed to both sequester beta amyloid in the peripheral CNS and facilitate brain clearance
  - Bapineuzumab's phase II data was impressive in the ApoE4 (-) cohort: Achieved SSI in 3 of 4 efficacy end points without an increased risk for vasogenic edema; Bapineuzumab's ph. III trial prospectively stratifies by ApoE4
  - Solanezumab's interim phase II data suggests an attractive safety profile (vs. Bapineuzumab) and pharmacodynamic effect (CSF and plasma biomarkers); Efficacy and dose response data is indeterminate; Phase III trials are not prospectively stratified by ApoE4 status
  - Phase I data from Gantenerumab, which targets both the mid domain and N-terminus, indicated strong dose response and rapid amyloid reduction; Vasogenic edema was a concern at a high dose and in ApoeE4 homozygotes, similar to Bapineuzumab
- Intravenous Immunoglobulins: Gammagard, albeit in an small phase II study, showed SSI, in both cognition and function, as well as lower brain ventricular enlargement rates; Baxter is funding a single phase III study which began enrolling in the second half of '10.



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# Executive Summary: Clinical Development Pipeline (2 of 2)

**What is the evidence for late stage assets?**

- Active Immunotherapies: Active immunotherapy offers substantial promise for amyloid oligomer clearance; 2nd generation vaccines, relative to Elan's original AN-1792, are posited to have cleaner immunogenicity profiles
- Gamma Secretase Inhibitors: Avagacestat (BMY), in phase II trials, is the most advanced gamma secretase inhibitor; 1st generation molecules were less selective, and the hope is that notch sparing, 2nd generation gamma secretase inhibitors will have less toxicity
  - Avagacestat is tolerable in lower doses (25 mg, 50mg) but higher doses (100 mg, 125 mg) had ~40% discontinuation rates due to gastrointestinal and dermatological side effects



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# The amyloid hypothesis has emerged, not without questions, as the consensus causative explanation for AD; Genetic linkages exist via ApoE mediated facilitation of beta amyloid degradation; In vitro studies show ApoE4 also increases phosphorylation of tau.

**Alternative Hypothesis**

- The cholinergic hypothesis posits that AD begins as a deficiency in the production of acetylcholine
  - Acetylcholine, which aids in cellular communication and stimulates brain activity, is degraded by AChE
  - Acetylcholine deficiencies are no longer seen as causal for AD and are thought to be a consequence of neuronal death
- The Tau hypothesis is support by empirical studies showing NFT load better correlates with AD progression than does amyloid plaque levels
  - NFT has been shown to be composed of abnormally hyperphosphorylated versions of the protein tau
  - The role of NFT in AD is not well understood, and it is unknown whether NFT is causal for AD or a consequence of AD

**Emerging Conesus**

- The Amyloid hypothesis is supported by majority opinion, albeit long-term declines in brain volumes with a vaccine (AN-1792) have been confounding and post-mortem histapathology studies are controversial
- It has long been hypothesized that beta amyloid concentration in the brain is AD's likely cause
  - APP is thought to play a role in synapse formation and cellular adhesion
  - Beta amyloid, derives from APP cleavage by either of two proteases, beta secretase or gamma secretase
  - Resultant AB42 is the focus, given it is less soluble and inhibits synaptic transmission by casein kinase 2 activation
  - It is believed beta amyloid concentration leads to neuro-degeneration and onset of AD
- Being an ApoE4 carrier is a key genetic risk factor for developing AD
  - ApoE4 is less efficient at degrading beta amyloid, as compared with ApoE3 and ApoE2
  - ApoE4 homozygotes are at 15 fold higher risk and ApoE4 heterozygotes are at 3 fold higher risk
  - In vitro, ApoE4 has increase p-tau, suggesting a consequential link between tau and beta amyloid
- Beta amyloid targeting strategies dominate the industry's clinical development pipeline, focused on: inhibiting synthesis, decreasing aggregation, and increasing removal, e.g.:
  - Passive immunotherapies (Monoclonal antibodies and Intravenous immunoglobulins), Active immunotherapies, Aggregation inhibitors, Neuronal restorers, Gamma secretase inhibitors, and Beta secretase inhibitors
- Tau targeting and Neuronal nicotinic receptor agonists are also being pursued, e.g.:
  - Phosphorylation inhibitors, Aggregation inhibitors, Alpha-4 beta-2 agonists, and Alpha-7 agonists



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Sources: Murdher, A.L. Alzheimer's disease-do tauists and baptists finally shake hands?. Trends Neurosci. 25(1), 2-26 (2002); Nistor, M. et al. Alpha- and beta-secretase activity as a function of age and beta-amyloid in Down syndrome and normal brain. Neurobiol Aging. 28(19), 1493-1506 (2007); Shen, Z.Z. Brain cholinesterases: II. The molecular and cellular basis of Alzheimer's disease. Med Hypotheses. 63(2), 308-321 (2004)

# Beta amyloid targeting strategies dominate the industry's clinical development pipeline, focused on: inhibiting synthesis, decreasing aggregation, and increasing removal; Tau targeting and Neuronal nicotinic receptor agonists are also being pursued.

## AD Pipeline: Current (N=69)

| Mechanism of Action | | US Reg./ Phase III (N=5) | Phase II (N=24) | Phase I (N=40) |
|---|---|---|---|---|
| Beta Amyloid Targeting (N=39) | Monoclonal Antibodies (N=8) | 2 | 3 | 3 |
| | Intravenous Immunoglobulins (N=3) | 1 | 2 | |
| | Active Immunotherapies (N=8) | | 3 | 3 |
| | Aggregation Inhibitors (N=3) | 1 | | 2 |
| | Neuronal Restorers (N=1) | | 1 | |
| | Gamma Secretase Inhibitors (N=8) | | 2 | 6 |
| | Beta Secretase Inhibitors (N=7) | | | 7 |
| | Other (N=3) | | | 3 |
| Tau Targeting (N=4) | Phosphorylation Inhibitors (N=2) | | 1 | 1 |
| | Aggregation Inhibitors (N=2) | | 1 | 1 |
| Glutamate Modulators (N=1) | | | 1 | |
| Serotonin Targeting (N=5) | 5-HT6 Antagonists (N=4) | | 1 | 3 |
| | 5-HT4 Agonists (N=1) | | 1 | |
| Neuronal Nicotinic Receptors (N=6) | Alpha-4 Beta-2 Agonists (N=3) | | 3 | |
| | Alpha-7 Agonists (N=3) | | 3 | |
| Rage Inhibitors (N=1) | | | 1 | |
| AChE Inhibitors (N=2) | | 1 | | 1 |
| Other (N=11) | | | 1 | 10 |



## AD Pipeline: Recent History

- Given a poorly understood etiology, multiple phase III assets have disappointed, e.g.:
  - Avandia (GSK)
  - Dimebon (PFE/MDVN)
  - Flurizam (MYGN)
  - Lipitor (PFE)
  - Semagacestat (LLY)
  - Zocor (MRK)
- AZD3480 (AZN/TRGT) in a large phase IIB study (N=567) failed to differentiate from placebo on ADAS-cog or CDR

## AD Pipeline: Upcoming Catalysts

- Solanezumab (LLY)
  - Interim phase III results, Q1 '12
  - Top line phase III results, H2 '12
- Bapineuzumab (PFE/JNJ/ELN)
  - Top line phase III results (US trials), H2 '12

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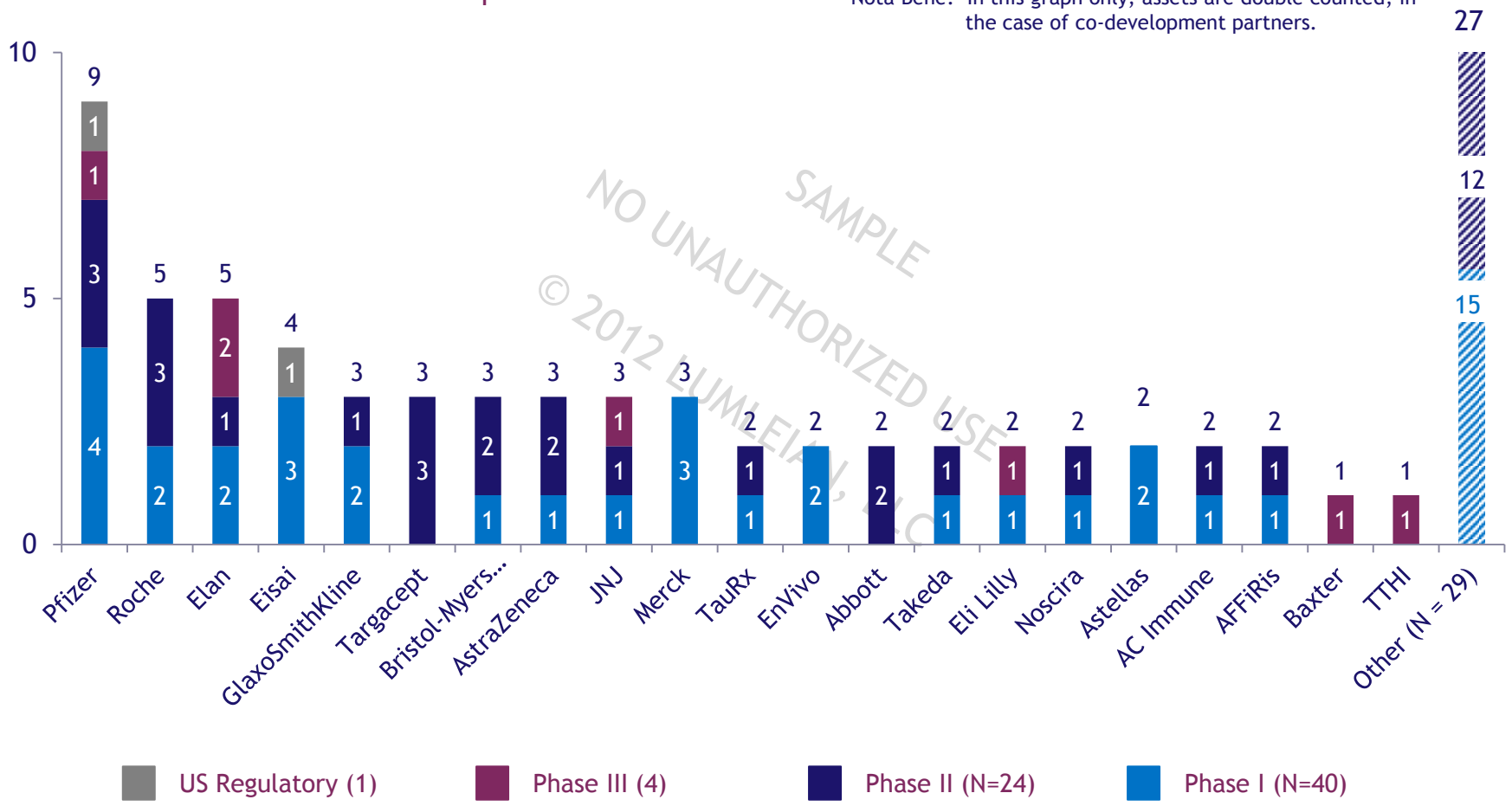
Sources: Lumleian estimates based on publicly available data from bio-pharmaceutical companies (financial statements, investor presentations, pipeline presentations, analyst day transcripts); 3rd party equity research reports; Bio-Pharma Insight; Clinical Trials.gov; CenterWatch

As of Q4 Lumleian validated 69 assets in 'active' clinical development for AD: 1 in US Regulatory, 4 in Phase III, 24 in Phase II, and 38 in Phase I; The leading sponsors are: Pfizer (9), Elan (5), Roche (5), Eisai (4), AstraZeneca (3), and Johnson & Johnson (3).

## AD Assets in 'Active' Clinical Development

Nota Bene: In this graph only, assets are double counted, in the case of co-development partners.



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Sources: Lumleian estimates based on publicly available data from bio-pharmaceutical companies (financial statements, investor presentations, pipeline presentations, analyst day transcripts); 3rd party equity research reports; Bio-Pharma Insight; Clinical Trials.gov; CenterWatch

# Beta amyloid MoAs include: Passive immunotherapies (Monoclonal antibodies, Intravenous immunoglobulins), Active immunotherapies, Aggregation inhibitors, Neuronal restorers, Gamma secretase inhibitors, and Beta secretase inhibitors.

| | Mechanism of Action | US Reg. / Phase III (N=5) | Phase II (N=24) | Phase I (N=40) |
|---|---|---|---|---|
| Beta Amyloid Targeting (N=39) | Monoclonal Antibodies (N=8) | • Bapineuzumab (PFE/JNJ/ELN)<br>• Solanezumab (LLY) | • Ponezumab (PFE)<br>• Gantenerumab (Roche/Chugai/MorphoSys)<br>• Crenzeumab (Roche/ AC Immune) | • 933776 (GSK)<br>• PF-05236812 (PFE, JNJ, ELN)<br>• BAN2401 (Eisai/BioArtic) |
| | Intravenous Immunoglobulins (N=3) | • Gammagard (BAX) | • Octagam (Octapharm)<br>• NewGam (Sutter Health) | |
| | Active Immunotherapies (N=6) | | • Vanutide Cridificar (PFE/JNJ/ELN)<br>• CAD106 (NVS/Cytos)<br>• AD02 (GSK/AFFiRiS) | • V950 (MRK)<br>• ACI-24 (AC Immune)<br>• AD03 (AFFiRis) |
| | Aggregation Inhibitors (N=3) | • Scyllo-inositol (ELN) | | • NP-61 (Noscira)<br>• Exebryl-1 (Proteotech) |
| | Neuronal Restorers (N=1) | | • PBT-2 (Prana) | |
| | Gamma Secretase Inhibitors (N=8) | | • Avagacestat (BMS)<br>• BMS708163 (BMS) | • Begacestat (PFE)<br>• MK-0752 (MRK)<br>• ELND-006 (ELN)<br>• E2212 (Eisai)<br>• NGP 555 (NeuroGenetic)<br>• GSM EVP-0962 (EnVivo) |
| | Beta Secretase Inhibitors (N=7) | | | • AZD3839 (AZN)<br>• MK-8931(MRK/Ligand)<br>• BACE Program (LLY)<br>• RG-7129 (Roche)<br>• CTS-21166 (CoMentis/Astellas)<br>• TAK-070 (Takeda)<br>• E2609 (Eisai) |
| | Other (N=3) | | | • NK-002 (Neurokine)*<br>• Memryte (Curaxis)<br>• Posiphen (QR Pharma) |



Notes: CAD106 - Payload antibody; Posiphen - APP/Aß and aSyn translational inhibitor; Memryte - Hypothalamic pituitary gonadal axis changes; NK-002 - Immunomodulator

Sources: Lumleian estimates based on publicly available data from bio-pharmaceutical companies (financial statements, investor presentations, pipeline presentations, analyst day transcripts); 3rd party equity research reports; Bio-Pharma Insight; Clinical Trials.gov; CenterWatch

# Other MoAs include Tau Targeting (Phosphorylation Inhibitors and Glutamatmate Modulators), Serotonin Targeting (5HT-6 Antagonists , 5HT-4 Antagonists Neuronal Nicotinic Receptors (Alpha-4 Beta-2 Antagonists, Alpha-7 Antagonists), Rage Inhibitors, and AChE Inhibitors.

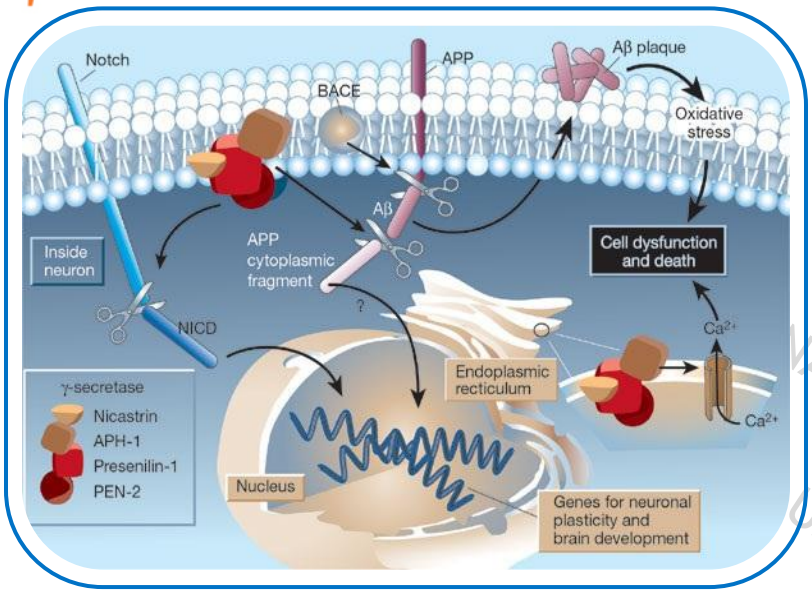
| Mechanism of Action | | US Reg. / Phase III (N=5) | Phase II (N=24) | Phase I (N=40) | |
|---|---|---|---|---|---|
| Tau Targeting (N=4) | Phosphorylation Inhibitors (N=2) | | • Nypta (Noscira) | • BMS241027 (BMS) | |
| | Aggregation Inhibitors (N=2) | | • Rember (TauRx) | • TAI (TauRx) | |
| Glutamate Modulators (N=1) | | | • EHT0202 (ExonHit) | | |
| Serotonin Targeting (N=5) | 5HT-6 Antagonists (N=4) | | • Lu-AE-58054 (Takeda/Lundbeck) | • SUVN-502 (Suven)<br>• AVN-322 (Avineuro)<br>• SB271046 (GSK) | |
| | 5HT-4 Antagonists (N=1) | | • PRX3140 (Nanotherapeutics) | | |
| Neuronal Nicotinic Receptors (N=6) | Alpha-4 Beta-2 Agonists (N=3) | | • AZD3480 (AZ/TRGT)<br>• AZD1446 (AZ/TRGT)<br>• ABT-089 (ABT) | | |
| | Alpha-7 Agonists (N=3) | | • MEM 63908 (Roche)<br>• EVP-6124 (EnVivo)<br>• TC-5619 (TRGT) | | |
| Rage Inhibitors (N=1) | | | • PF-4494700 (PFE) | | |
| AChE Inhibitors (N=2) | | • Aricept transdermal (PFE/Eisai) | | • SNX-001 (SeneXta) | |
| Other (N=11) | | | • ABT 384 (ABT) | • RG1577 (Roche/Evotec)<br>• APH-0703 (Aphios)<br>• AZD-5213 (AZN<br>• MT-4666 (Mitsubishi)<br>• PF-04995274 (PFE) | • mGluR2 program (Addex)<br>• ASP0777 (Astellas)<br>• MCD-386 (Mithridion)<br>• NsG-0202 (NsGene)<br>• PF-05212377 (PFE) |



Notes: RG1577 - MAO-B inhibitor; APH-0703 - Protein Kinase C Delta activator; AZD-5213 - H3AN modulators; MCD-386 - Muscarinic agonists; MT-4666 - AChR agonists; NsG-0202 - AChR agonists

Sources: Lumleian estimates based on publicly available data from bio-pharmaceutical companies (financial statements, investor presentations, pipeline presentations, analyst day transcripts); 3rd party equity research reports; Bio-Pharma Insight; Clinical Trials.gov; CenterWatch

# Bapineuzumab (PFE/JNJ/ELN) and Solanezumab (LLY), are the most advanced Beta Amyloid Targeting Monoclonal Antibodies; Bapineuzumab targets the N-terminus and is believed to both sequester beta-amyloid in the peripheral CNS and facilitate brain clearance.




**Physiology**

- Beta amyloid is a peptide, processed from APP, which is associated with activation of kinase enzymes, functions as a transcription factor and exhibits anti-microbial activity
  - In AD patients, beta amyloid is the primary component of amyloid plaques, which induce neuronal death

**Hypothesized Mechanism**

- Sequesters beta amyloid in the peripheral CNS and facilitates clearance of beta amyloid from the brain
  - Bapineuzumab targets the N-terminus of the beta amyloid peptide, and is believed to both sequester beta amyloid in the peripheral CNS and facilitate clearance of from the brain
  - Solanezumab targets the C-terminus and is thought to act only by sequestering beta-amyloid in the peripheral CNS; It is hypothesized to have a better safety profile
  - Ponezumab targets the mid domain
  - Gantenerumab targets the mid domain and N-terminus
  - It is thought that IVIG contains naturally occurring antibodies which recognize amyloid



## Pipeline

| | Monoclonal Antibodies | Intravenous Immunoglobulin |
|---|---|---|
| Phase III | • Bapineuzumab (PFE/JNJ/ELN)<br>• Solanezumab (LLY) | • Gammagard (BAX) |
| Phase II | • Ponezumab (PFE)<br>• Gantenerumab (Roche/MorphoSys) | • Octagam (Octapharm)<br>• NewGam (Sutter Health) |
| Phase I | • 933776 (GSK)<br>• R1450 (Roche)<br>• PF-05236812 (PFE)<br>• BAN2401 (Eisai/BioArtic) | |

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Sources: Woodhouse, A. et al. Vaccination strategies for Alzheimer's disease: A new hope?". Drugs & Aging. 24 (2), 107-119 (2007)

# Bapineuzumab's phase II data was impressive in the ApoE4 (-) cohort: Achieved SSI in 3 of 4 efficacy end-points without an increased risk for vasogenic edema; Bapineuzumab's ph. III trial prospectively stratifies by ApoE4.

| | Clinical Results (Phase II) |
|---|---|
| Efficacy: | • Failed to achieve SSI in either primary end-point using MITT: ADAS-cog (cognition), DAD (function)<br>– Achieved SSI in three of four end-points in CA: ADAS-cog & NTB (cognition), DAD (function)<br>• ApoE4 neg. sub-group had SSI in 3 of 4 end-points using MITT and CA: ADAS-cog & NTB (cognition) CDR-sb (function)<br>– ApoE4 pos. failed to achieve SSI all 4 end-points using MITT and CA |
| Safety: | • Vasogenic edema signals in ApoE4 pos. cohort treated with higher doses |
| Dose Response: | • Lack of dose response, particularly 1.0 mg/kg |
| Lumleian Commentary: | • MMSE discrepancy in ApoE4 neg. cohort: placebo vs. Bapineuzumab; Steep ADAS-cog decline in placebo group; A subcutaneous formulation (posited to reduce vasogenic edema) is enrolling for Phase III trials |

| | Phase II Program (Completed) | Phase III Program (Ongoing) |
|---|---|---|
| Patient Segment: | • Mild to Moderate AD | • Mild to Moderate AD |
| Stratification: | • Post-hoc: ApoE4 carrier; ApoE4 non-carrier | • Prospective: ApoE4 carrier; ApoE4 non-carrier<br>• Post-hoc: Mild AD, Moderate AD |
| Studies: (Target Enrollment) | • Single phase II (N=234) | • US ApoE4 neg. (N=1,030); US ApoE4 pos. (N=800); Global ApoE4 neg. (N=1,030); Global ApoE4 pos. (N=800) |
| Comparator: | • Placebo | • Placebo |
| Dosing: | • 0.15; 0.5; 1.0; 2.0 mg/kg IV every 3 months | • 0.5 (all trials); 1.0 mg/kg (ApoE4 neg. trials) IV every 3 months |
| Duration: | • 18 months | • 18 months |
| Primary End-Points: | • Cognition: ADAS-cog (NTB)<br>• Function: DAD (CDR-sb) | • Cognition: ADAS-cog or NTB (unspecified)<br>• Function: DAD or CDR-sb (unspecified) |

Notes: In April '09 the sponsors announced elimination of the 2.0 mg/kg dosing cohorts from the two ApoE4 carrier trials with enrolled patients being assigned to the 1.0 mg/kg cohort and newly recruited patients being randomized to either the 0.5 mg/kg or the 1.0 mg/kg cohorts; In parallel the original targets of 1250 per trial were reduced to 1030 per trial

Sources: IACD presentation (2008); Company press releases; 3rd party equity research reports; Bio-Pharma Insight; Clinical Trials.gov; Centerwatch; Salloway, S., R. Sperling, and S. Gilman et al. "A Phase 2 Multiple Ascending Dose Trial of Bapineuzumab in Mild to Moderate Alzheimer Disease." *Neurology* 73.24 (2009): 2061-070

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# Solanezumab's interim phase II data suggests an attractive safety profile (vs. Bapineuzumab) and pharmacodynamic effect (CSF and plasma biomarkers); Efficacy and dose response data is indeterminate; Phase III trials are not prospectively stratified by ApoE4 status.

| | Clinical Results (Phase II) |
|---|---|
| Efficacy: | • Demonstrated increased beta amyloid levels in CSF and plasma, suggest Solanezumab mobilizes beta amyloid in plaques and normalizes soluble CSF beta amyloid<br>- Subsequently, a correlation was established between plasma beta-amyloid amyloid burden using single PET with IMPY<br>- No effect was shown on CSF t-tau and p-tau<br>• No clinical efficacy or dose response has been shown, given the 12 week duration of the initial interim phase II data |
| Safety: | • No reports of treatment-related vasogenic edema, infusion reactions or meningoencephalitis |
| Dose Response: | • Indeterminate |
| Lumleian Commentary: | • Interim phase III data reads out in Q1 '12 with top line phase III results in H2 '12; Lack of ApoE4 stratification |

| | Phase II Program (Completed) | Phase III Program (Ongoing) |
|---|---|---|
| Patient Segment: | • Mild to Moderate AD | • Mild to Moderate AD |
| Stratification: | | • Post-hoc: ApoE4 carrier; ApoE4 non-carrier |
| Studies: (Target Enrollment) | • Single phase II (N=52), Sub-Study (N=24)<br>• Open label study in Japan (N=33) | • EXPEDITION 1 (N=1,000); 1:1 arms; Global<br>• EXPEDITION 2 (N=1,000); 1:1 arms; Global |
| Comparator: | • Placebo | • Placebo |
| Dosing: | • 100; 400 mg/kg IV every week<br>• 100; 400 mg/kg IV every month | • 100; 400 mg/kg IV every month |
| Duration: | • 12 weeks | • 18 months |
| Primary End-Points: | • Cognition: ADAS-cog<br>• Function: NA | • Cognition: ADAS-cog<br>• Function: ADCS-ADL |

Notes: In January '11 Lilly announced that one patient in phase III trials had developed vasogenic edema, but did not specify if this was in the Solanezumab or placebo arm

Sources: IACD presentation (2008); Company press releases; 3rd party equity research reports; Bio-Pharma Insight; Clinical Trials.gov; Centerwatch; Siemers, E. R., S. Friedrich, and R. A. Dean, et al. "Safety and Changes in Plasma and Cerebrospinal Fluid Amyloid Beta after a Single Administration of an Amyloid Beta Monoclonal Antibody in Subjects with Alzheimer Disease." *Clinical Neuropharmacology* 33.2 (2010): 67-73.; Siemers , E. R., R. B. Demattos, F. Stuart et al., "Use of a Monoclonal Anti-A Antibody with Biochemical and Imaging Biomarkers To Determine Amyloid Plaque Load in Patients with Alzheimer's Disease (AD) and Control Subjects," American Academy of Neurology 61st Annual Meeting; April 25-May 2, 2009; Seattle, WA. Abstract IN3-2.009.

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# Phase I data from Gantenerumab, which targets both the mid domain and N-terminus, indicated strong dose response and rapid amyloid reduction; Vasogenic edema was a concern at a high dose and in ApoeE4 homozygotes, similar to Bapineuzumab.

| | Clinical Results (Phase I) |
|---|---|
| Efficacy: | • SS amyloid reduction in patients treated with Gantenerumab: Mean percent change in cortical brain amyloid level from baseline difference, relative to placebo, was -15.6% (low dose) group and -35.7% (high dose)<br>- In ex vivo studies Gantenerumab induced phagocytosis of amyloid, in a dose-dependent manner, supporting the hypothesis of amyloid clearance microglia-mediated phagocytosis |
| Safety: | • 2 cases of vasogenic edema in patients treated with the high dose (N=6); Both were ApoE4 homozygotes (carriers ) |
| Dose Response: | • Amyloid reduction and vasogenic edema were dose dependent |
| Lumleian Commentary: | • Rapid amyloid reduction (7 months); Pooled SS was driven in large part by high dose arm, in which safety was a concern (e.g. vasogenic edema) |

| | Phase I Program (Completed) | Phase II Program (Ongoing) |
|---|---|---|
| Patient Segment: | • Mild to Moderate AD | • Prodromal AD |
| Studies: (Target Enrollment) | • Prospective: ApoE4 carrier; ApoE4 non-carrier | |
| Comparator: | • Single phase II (N=18), with 6 receiving 60 mg, 6 receiving 200 mg, and 4 on placebo | • Single phase IIB (N=360) |
| Dosing: | • Placebo | • Placebo |
| Duration: | • 60 mg; 200 mg/kg IV monthly | • 105 mg; 225 mg subcutaneous monthly |
| Primary End-Points: | • 7 months | • 26 months |
| Patient Segment: | • Cortical brain amyloid level (PiB PET) | • Cognition: CDR-sob<br>• Function: CDR-sob |



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Sources: Ostrowitzki, S. et al. Mechanism of amyloid removal in patients with Alzheimer disease treated with Gantenerumab. Arch Neurol. Published Online October 10, 2011. Doi:10.1001/Archneurol.2011.1538; Company press releases; 3rd party equity research reports; Bio-Pharma Insight; Clinical Trials.gov; Centerwatch

## Gammagard, albeit in an small phase II study, showed SSI, in both cognition and function, as well as lower brain ventricular enlargement rates; Baxter is funding a single phase III study which began enrolling in the second half of '10.

| | Clinical Results (Phase II) |
|---|---|
| Efficacy | • Patients treated with Gammagard had an SSI in ADAS-cog and ADCS-CGIC after18 months and SS lower brain ventricular enlargement rates, which were correlated with outcomes<br>– Lower whole brain atrophy rates were observed but were not SS |
| Safety | • Well tolerated; Most common AEs were rash and non-hemolytic anemia |
| Dose Response | • Brain ventricular enlargement rates were correlated with dosing |
| Lumleian Commentary | • Results (cognition, function, and ventricular enlargement) are a positive surprise in the context of a small sample size and that the comparator group also received Gammagard for 12 months |

| | Phase II Program | Phase III Program |
|---|---|---|
| Patient Segment | • Mild to Moderate AD | • Mild to Moderate AD |
| Studies (Target Enrollment) | • Single phase II (N=24), with 16 receiving Gammagard uninterrupted | • Single Phase III, Gap Study, (N=390), with two-thirds of participants in Gammagard arm and one-third in placebo arm |
| Comparator | • Placebo (6 months) followed by Gammagard 12 months | • Placebo |
| Dosing | • Range: 0.2g/kg every 2 weeks to 0.8 g/kg every 4 weeks | • 400 mg/kg IV every 2 week<br>• 200 mg/kg IV every 2 week |
| Duration | • 18 months | • 18 months |
| Primary End-Points | • Cognition: ADAS-cog<br>• Function: ADCS-CGIC | • Cognition: ADAS-cog<br>• Function: ADCS-CGIC |



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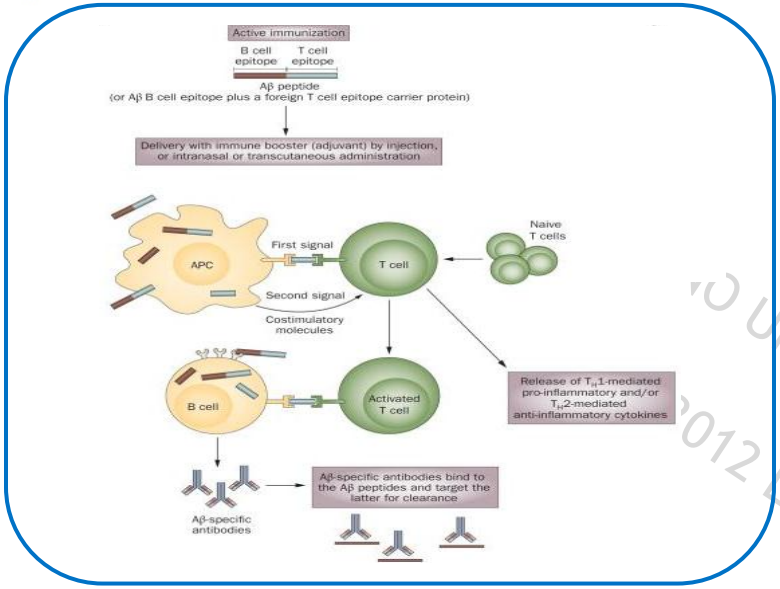
Sources: Company press releases; 3rd party equity research reports; Bio-Pharma Insight; Clinical Trials.gov; Centerwatch; Tsakanikas, D. and N. Relkin, "Neuropsychological Outcomes Following 18-Months of Uninterrupted Intravenous Immunoglobulin Treatment in Patients with Alzheimer's Disease (AD)," American Academy of Neurology 62nd Annual Meeting: April 10-17, 2010; Toronto, Ontario, Canada. Abstract S34.005.

# Active immunotherapy offers substantial promise for amyloid oligomer clearance; 2nd generation vaccines, relative to Elan's original AN-1792, are posited to have cleaner immunogenicity profiles.




**Physiology**

- Active immunotherapy (vaccination) introduces an antigen which mimics amyloid beta
- Antibodies targeting this antigen are produced and subsequently bind to amyloid beta facilitating microglial activation and oligomer clearance

**Hypothesized Mechanism**

- AN-1792, Elan's original vaccine, was promising, until ~6% of phase II participants developed meningoencephalitis
  - After a year, 20% of patients generated an immune response had a SSI in NTB cognition
  - After 4.5 years, SSI was observed in specific NTB subsets as well as on DAD
- Vanutide Cridificar, a 2nd generation vaccine, offers a cleaner immunogenicity profile, based on exclusion of a T-cell epitope, linked to meningoencephalitis



## Pipeline

**Phase II**

- Vanutide Cridificar (PFE/JNJ/ELN)
- CAD106 (NVS/Cytos)
- AD02 (GSK/AFFiRiS)

**Phase I**

- V950 (MRK)
- ACI-24 (AC Immune)
- AD03 (AFFiRis)

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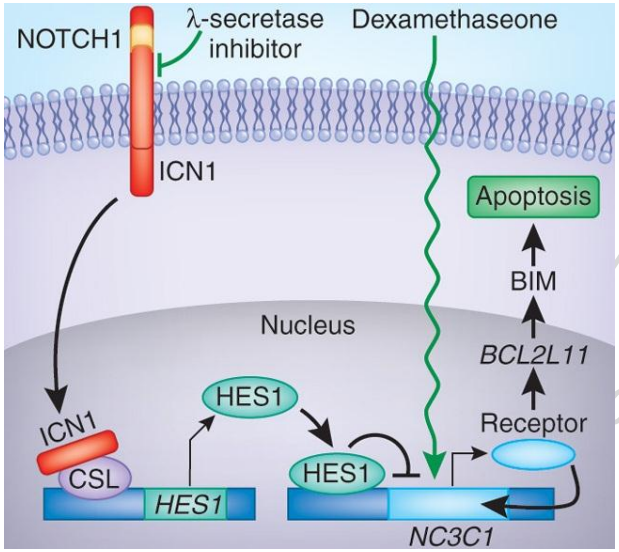
Sources: Lemere, C.A. et al. Can Alzheimer disease be prevented by amyloid-beta immunotherapy?. Nat Rev Neurol. 6(2), 108-119 (2010)

Avagacestat (BMY), in phase II trials, is the most advanced 2nd generation gamma secretase inhibitor; 1st generation molecules were less selective, and the hope is that notch sparing, 2nd generation gamma secretase inhibitors will have less toxicity.




| | |
|---|---|
| Physiology | • Gamma secretase is an inter-membrane protease that cleaves single pass trans membrane proteins, including APP, at residues within the trans- membrane domain |
| Pathophysiology | • In AD patients, Gamma secretase cleaves APP, which promotes amyloid plaque formation |
| Hypothesized Mechanism | • Reduces amyloid plaque formation through blockage of gamma secretase function<br>- Lilly's Semagacestat, which has an affinity for notch protein and a narrow therapeutic index, was halted in ph. III trials due to poor efficacy and safety concerns, e.g. skin cancer<br>- Avagacestat has been shown to be tolerable in lower doses but higher doses had high discontinuation rates and suggested an increased risk for skin cancer<br>- BMS708163 has been shown to be tolerable at doses below100 mg/day but not at higher doses |



## Pipeline

| | |
|---|---|
| Phase II | • Avagacestat (BMY)<br>• BMS708163 (BMY) |
| Phase I | • Begacestat (PFE)<br>• MK-0752 (MRK)<br>• ELND-006 (ELN)<br>• E2212 (Eisai)<br>• NGP 555 (NeuroGenetic)<br>• GSM EVP-0962 (EnVivo) |

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Sources: Grosveld, G.C. Gamma secretase inhibitors: notch so bad. Nat Med. 15(1), 20-21 (2009)

## Avagacestat is tolerable in lower doses (25 mg, 50mg) but higher doses (100 mg, 125 mg) had ~40% discontinuation rates due to gastrointestinal and dermatological side effects; An ongoing phase II trial is investigating a lower dose (50 mg) in prodromal AD.

| | Clinical Results (Phase II) |
|---|---|
| Efficacy | • Although the phase II study was not powered to determine efficacy, little difference was seen between the treatment and placebo arms at lower doses (25 mg, 50mg)<br>- Higher doses (100mg, 125 mg) indicated a potential for negative cognitive effects |
| Safety | • Lower doses (25 mg, 50mg) were tolerable but higher doses (100 mg, 125 mg) had ~40% discontinuation rates due to gastrointestinal and dermatological (rash and itching) side effects<br>- Phase II data also showed an increased risk of non-melanoma skin cancer, similar to Lilly's Semagacestat |
| Dose Response | • Tolerability was correlated with dosing |
| Lumleian Commentary | • Phase II results were somewhat disappointing given Avagacestat is a notch-sparing gamma secretase inhibitor<br>• Avagacestat is investigating the prodromal AD segment |

| | Phase II Program (Completed) | Phase II Program (Ongoing) |
|---|---|---|
| Patient Segment | • Mild to Moderate AD | • Prodromal Alzheimer's Disease |
| Studies (Target Enrollment) | • Single Phase II (N=209) | • Single Phase II (N=270) |
| Comparator | • Placebo | • Placebo |
| Dosing | • 25mg QD, 50 mg QD<br>• 100mg QD, 125mg QD | • 50mg QD |
| Duration: | • 36 weeks (24 weeks dosing) | • 104 weeks (24 weeks dosing) |
| Primary End-Points: | • Primary: Adverse Events<br>• Secondary: Pharmacodynamics | • Primary: Adverse Events<br>• Secondary: CSF biomarkers |

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Sources: Company press releases; 3rd party equity research reports; Bio-Pharma Insight; Clinical Trials.gov; Centerwatch

# A number of additional assets are in phase II/III development but lack any clinical efficacy data, albeit Nypta (Noscira) and PBT-2 (Prana) did show relatively strong efficacy signals.

| | Mechanism of Action | Phase | Efficacy Data | Safety Data |
|---|---|---|---|---|
| Scyllo-inositol (ELN) | • Aggregation Inhibitors (Amyloid Beta Targeting) | •III | • Did not achieve SSI on NTB and ADCS-ADL endpoints after 18 months<br>• Confirmed biologic activity on amyloid beta and achieved targeted CSF concentrations | • 250 mg dose BID demonstrated acceptable safety profile |
| PBT-2 (Prana) | • Neuronal Restorers | • II | • PBT-2 reduced amyloid beta levels in the CSF of patients on the 250mg dose<br>• NTB was significantly improved for patients on the 250mg dose | • Safe and well tolerated at the 250 mg dose in phase IIA trial |
| Nypta (Noscira) | • Phosphorylation Inhibitors (Tau Targeting) | • II | • Positive effect (not significant) seen on 4 of 5 end-points (short duration of 20 weeks, not powered for efficacy) | • Safe and well tolerated in phase IIA trial |
| EHT0202 (ExonHit) | • Glutamate Modulators | • II | • No significant differences were seen between treatment groups (short duration of 3 months, not powered for efficacy) | • Dose-dependent numbers of early withdrawal and CNS related adverse events were observed |
| AZD3480 (AZ/TRGT) | • Alpha-7 Agonists (Neuronal Nicotinic Receptors) | • II | • Failed to achieve SSI on ADAS-cog or CDR in large phase IIB trial<br>• No direct dose response | • Safe and well tolerated in phase IIA trial |
| PF-4494700 (PFE) | • Rage Inhibitors | • II | • Dose dependent increase in AB40 but not AB42<br>• No significant efficacy endpoints | • Safe at 5mg QD (initiated at 15mg)<br>• Dropped phase II 20 mg QD (initiated at 60 mg) |

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Sources: Company press releases; 3rd party equity research reports; Bio-Pharma Insight; Clinical Trials.gov; Centerwatch

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# Executive Summary: Commercial Landscape

| | |
|---|---|
| How large is the global market and what growth is forecast? | • Global '11 brand revenue fell 22.6% to ~$5.7B versus '10, driven by US generic donepezil penetration; The market is forecast to plateau through '15, with the anticipated launches of the first anti beta amyloid monoclonal antibodies offsetting generic penetration<br>- US: United States '10 brand revenue was ~$3.9B and shrank by ~50% to $2.0B in '11; Including pipeline revenue, brand revenue is forecast to grow at ~6.7% annually between '12 and '15<br>- EU: European '11 brand revenues was ~$1.6B and is forecast to shrink by ~8.6% annually between '12 and '15, driven by patent expiries<br>- JP: Japan '11 brand revenues was ~$1.5B and is forecast to grow by ~23.5% between '11 and '12 driven by Aricept growth and recent launches (e.g. Namenda, Exelon, Razadyne), but shrink by ~5.1% between '12 and '15 due to Aricept patent expiry in 06/13<br>- RW: Rest of world '11 brand revenue was ~$700M and is forecast to grow by ~1.4% between '12 and '15 |
| What are launch forecasts? | • Wall Street consensus estimates forecast new product launches will increase the '15 global market by ~$700M, driven largely by anticipated launches for Pfizer/JNJ/Elan's Bapineuzumab and Eli Lilly's Solanezumab |
| What trends are driving the US market? | • In Q4 '11 US AD retail revenue fell ~37.6% driven by a ~41.8% decline in product mix, due to the large shift to generic donepezil; Days of therapy grew ~4.5% in parallel with total prescription volume<br>- Mix: In the US generics now command ~55% share of total prescription volume; More than 90% of Aricept Rx has shifted to generic donepezil since November 2010; Namenda and Exelon patch, respectively maintain relatively stagnant ~33% and ~8.5% shares<br>- Price: The average cost per a day of therapy is $4.02 and decreased by ~40% in 2011; The cost per day of therapy with Donepezil declined by ~77.5% in 2011 and the cost per day of therapy with Exelon patch and Namenda increased by ~9% and ~15% respectively<br>- Promotion: In the three months ending October '11 total promotional spend grew ~1.8%; Healthcare professional spend fell ~5.4% as Aricept and Namenda reduced sales forces in line with Aricept loosing exclusivity; Aricept substantially increased DTC investment for its 23mg formulation |



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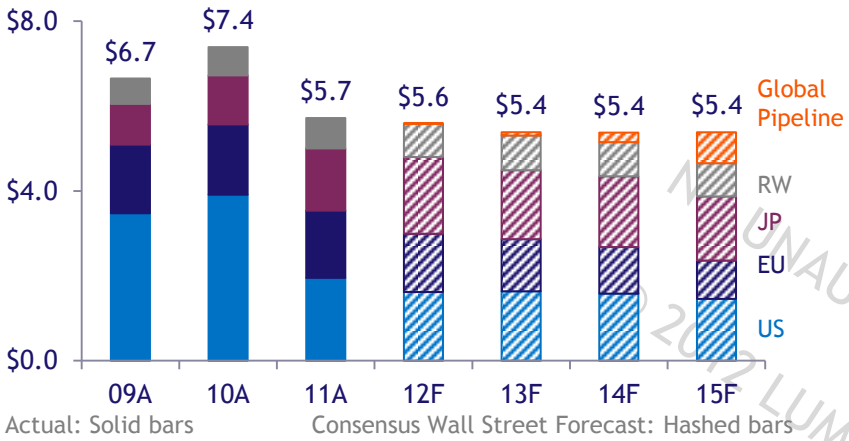
# Global '11 brand revenue fell 22.6% to ~$5.7B versus '10, driven by US generic donepezil penetration; The market is forecast to plateau through '15, with the anticipated launches of the first anti beta amyloid monoclonal antibodies offsetting generic penetration.

## Alzheimer's Global Brand Revenue ($B)

Updated: 02/15/12




Actual: Solid bars  Consensus Wall Street Forecast: Hashed bars

| | '11 Sales ($B) | '10-'11A CAGR | '11-'12F CAGR | '12-'15F CAGR |
|---|---|---|---|---|
| Global & Pipeline | $5.7 | -22.6% | -2.2% | -1.2% |
| US | $2.0 | -50.1% | -17.0% | 6.7% |
| EU | $1.6 | -4.4% | -13.3% | -8.6% |
| JP | $1.5 | 26.9% | 23.5% | -5.1% |
| RW | $0.7 | 7.5% | 9.6% | 1.4% |

### Baseline Epidemiological Growth (Prevalence)

- US: 2.5%
- EU: 1.7%
- JP: 3.2%

### Recent and Anticipated New Product Launches - Global

- Pfizer/JNJ/Elan's Bapineuzumab ('13)
- Baxter's Gammagard ('12)
- Eli Lilly's Solanezumab ('13)
- Pfizer's PF-4494700 ('15)
- Pfizer/JNJ/Elan's Vanutide Cridificar ('15)

### Recent and Anticipated New Product Launches - Japan

- Exelon (04/11), Namenda/Memary (01/11), Razadyne (01/11)

### Recent and Anticipated Line Extensions

- US: Aricept - 23mg (07/10); Namenda XR (07/10) but not yet launched due to patent litigation
- JP: Aricept - Jelly (07/09)

### Recent and Anticipated Loss of Exclusivity

- US: Aricept (11/10), Exelon Patch (08/12), Namenda (04/15)
- EU: Exelon (2012-13), Aricept (2012-13)
- JP: Aricept (06/13)



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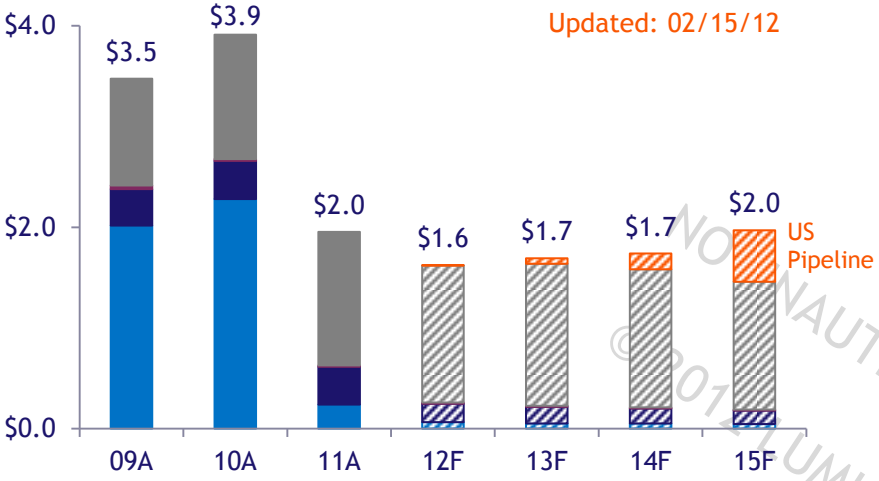
Notes: Branded sales excludes generic revenues; Pipeline includes: Bapineuzumab ('13), Gammagard ('12), Solanezumab ('13), PF-4494700 ('15), Vanutide Cridificar ('15)

Sources: Lumleian estimates based on publicly available data from bio-pharmaceutical companies (financial statements, investor presentations, analyst day transcripts); 3rd party equity research reports; Bio-Pharma Insight

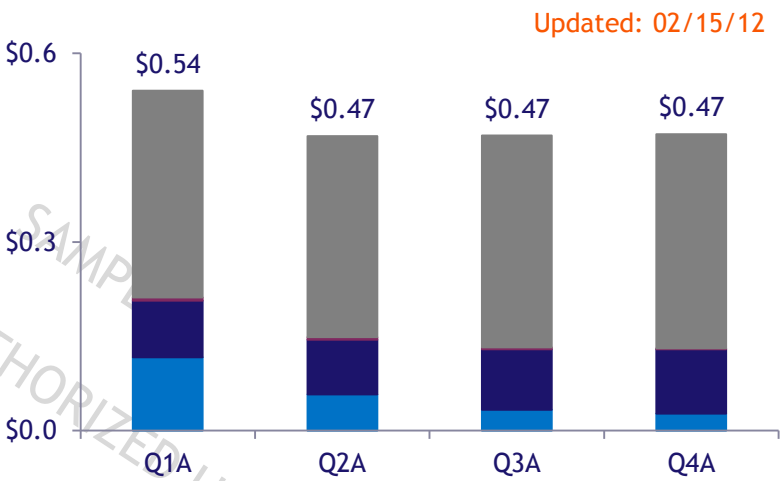
# United States '10 brand revenue was ~$3.9B and shrank by ~50% to $2.0B in '11; Including pipeline revenue, brand revenue is forecast to grow at ~6.7% annually between '12 and '15.

Alzheimer's United States Brand Revenue ($B)




Actual: Solid bars  Wall Street Consensus Forecast: Hashed bars

2011 Alzheimer's United States Brand Revenue ($B)




Actual: Solid bars  Wall Street Consensus Forecast: Hashed bars



| | '11 Revenue ($B) | '10-'11A CAGR | '11-'12F CAGR | '12-'15F CAGR |
|---|---|---|---|---|
| United States | $2.0 | -50.1% | -17.0% | 6.7% |
| Aricept | $0.2 | -89.5% | -73.2% | -11.1% |
| Exelon | $0.4 | -1.1% | -51.2% | -9.9% |
| Namenda | $1.3 | 7.3% | 2.6% | -2.3% |

| | Q4 Revenue ($B) | Q3A-Q2A CAGR | Q3A-Q4A CAGR |
|---|---|---|---|
| United States | $0.47 | 0.2% | 0.5% |
| Aricept | $0.03 | -42.0% | -18.8% |
| Exelon | $0.10 | 10.3% | 6.3% |
| Namenda | $0.34 | 5.3% | 1.1% |

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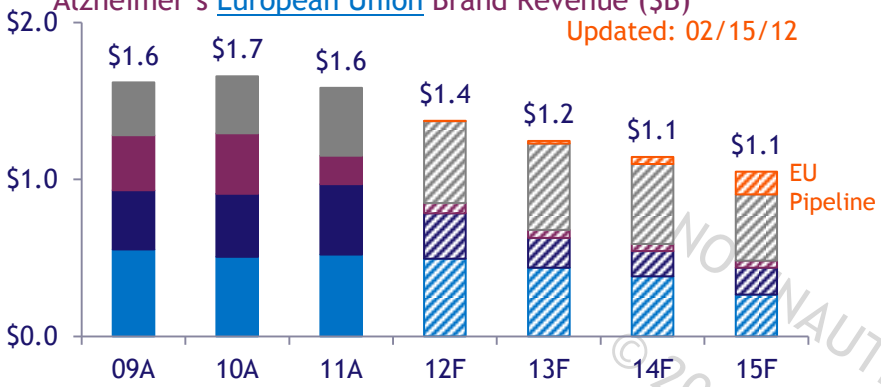
Notes: Branded sales excludes generic revenues; Pipeline includes: Bapineuzumab ('13), Gammagard ('12), Solanezumab ('13), PF-4494700 ('15), Vanutide Cridificar ('15)

Sources: Lumleian estimates based on publicly available data from bio-pharmaceutical companies (financial statements, investor presentations, analyst day transcripts); 3rd party equity research reports; Bio-Pharma Insight

European Union ’11 brand revenues was ~$1.6B and is forecast to shrink by ~8.6% annually between ‘12 and ‘15, driven by patent expiries; Japan ‘11 brand revenues was ~$1.5B and is forecast to grow by ~23.5% between ‘11 and ‘12 driven by Aricept growth and recent launches, but shrink by ~5.1% between ‘12 and ‘15 due to Aricept patent expiry in 06/13.

## Alzheimer’s European Union Brand Revenue ($B)

Updated: 02/15/12

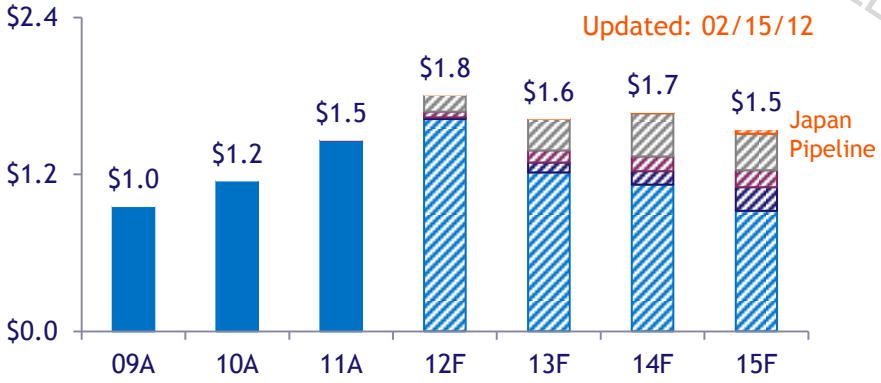



Actual: Solid bars  Wall Street Consensus Forecast: Hashed bars

| | ’11 Revenue ($B) | ’10-’11A CAGR | ’11-’12F CAGR | ’12-’15F CAGR |
|---|---|---|---|---|
| European Union | $1.6 | -4.4% | -13.3% | -8.6% |
| Aricept | $0.5 | 2.7% | -5.2% | -18.6% |
| Exelon | $0.4 | 11.8% | -35.5% | -16.1% |
| Razadyne | $0.2 | -53.2% | -63.9% | -11.5% |
| Namenda | $0.4 | 19.6% | 20.8% | -7.0% |

## Alzheimer’s Japan Brand Revenue ($B)

Updated: 02/15/12




Actual: Solid bars  Wall Street Consensus Forecast: Hashed bars

| | ’11 Revenue ($B) | ’10-’11A CAGR | ’11-’12F CAGR | ’12-’15F CAGR |
|---|---|---|---|---|
| Japan | $1.5 | 26.9% | 23.5% | -5.1% |
| Aricept | $1.5 | 26.4% | 11.2% | -17.2% |
| Exelon | $0.0 | | | 134.7% |
| Razadyne | $0.0 | | | 45.7% |
| Namenda | $0.0 | | | 28.5% |



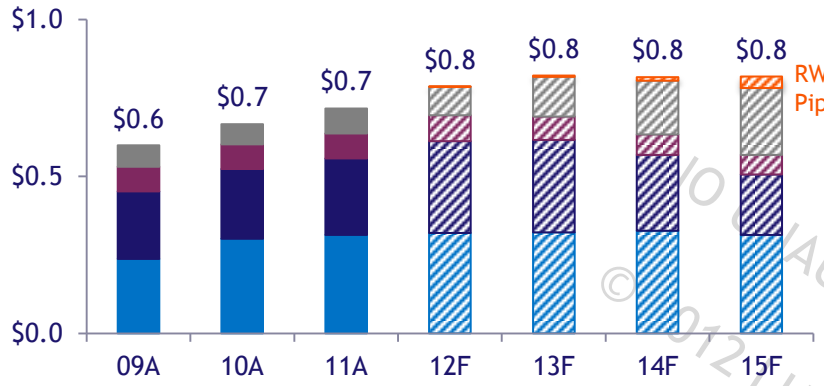
Notes: Branded sales excludes generic revenues; Pipeline includes: Bapineuzumab (’13), Gammagard (‘12), Solanezumab (’13), PF-4494700 (’15), Vanutide Cridificar (’15)

Sources: Lumleian estimates based on publicly available data from bio-pharmaceutical companies (financial statements, investor presentations, analyst day transcripts); 3rd party equity research reports; Bio-Pharma Insight

# Rest of world ‘11 brand revenue was ~$700M and is forecast to grow by ~1.4% between ‘12 and ‘15.

## Alzheimer’s Rest of World Brand Revenue ($B)

Updated: 02/15/12




| | ’11 Revenue ($B) | ’10-’11A CAGR | ’11-’12F CAGR | ’12-’15F CAGR |
|---|---|---|---|---|
| Rest of World | $0.7 | 7.5% | 9.6% | 1.4% |
| Aricept | $0.3 | 4.1% | 2.0% | -0.6% |
| Exelon | $0.2 | 9.2% | 20.4% | -13.1% |
| Razadyne | $0.1 | 2.6% | 2.5% | -8.4% |
| Namenda | $0.1 | 23.8% | 13.9% | 32.8% |

Actual: Solid bars  Wall Street Consensus Forecast: Hashed bars



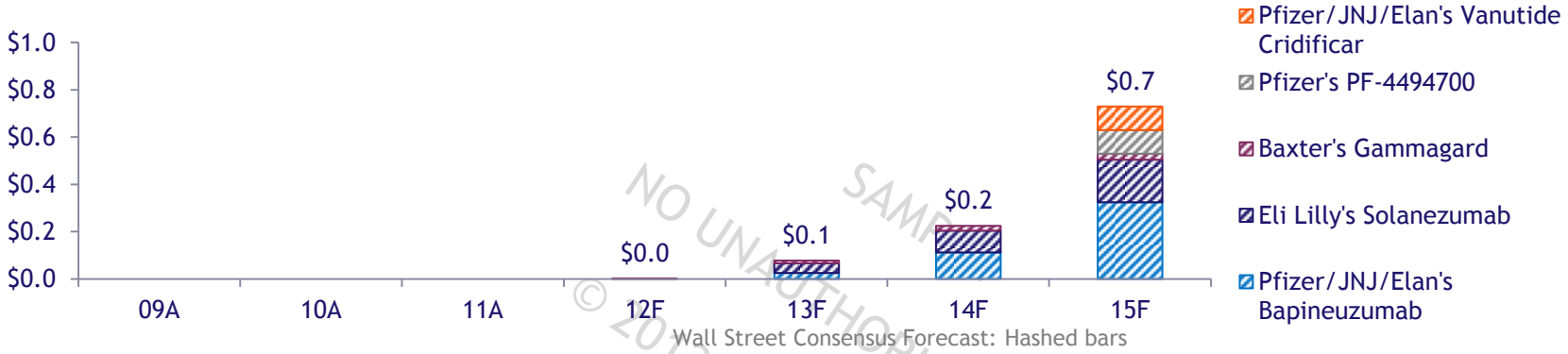
Notes: Branded sales excludes generic revenues; Pipeline includes: Bapineuzumab (’13), Gammagard (‘12), Solanezumab (’13), PF-4494700 (’15), Vanutide Cridificar (’15)

Sources: Lumleian estimates based on publicly available data from bio-pharmaceutical companies (financial statements, investor presentations, analyst day transcripts); 3rd party equity research reports; Bio-Pharma Insight

# Wall Street consensus estimates forecast new product launches will increase the '15 global market by ~$700M, driven largely by anticipated launches for Pfizer/JNJ/Elan's Bapineuzumab and Eli Lilly's Solanezumab.

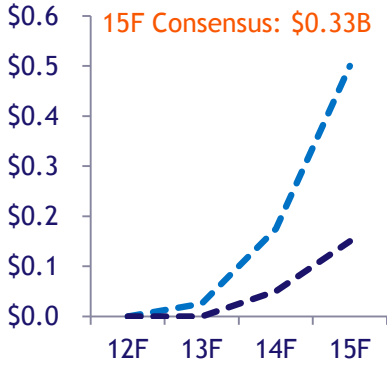
## Global Pipeline Assets Wall Street Consensus Forecast ($B)

Updated: 02/15/12

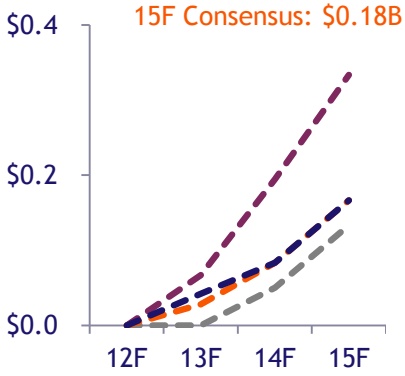




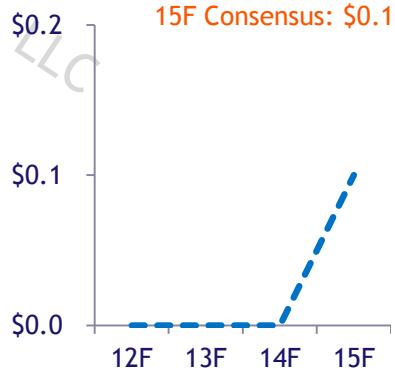

## Global Bapineuzumab Equity Research Forecasts ($B)




## Global Solanezumab Equity Research Forecasts ($B)




## Global PF-4494700 Equity Research Forecasts ($B)

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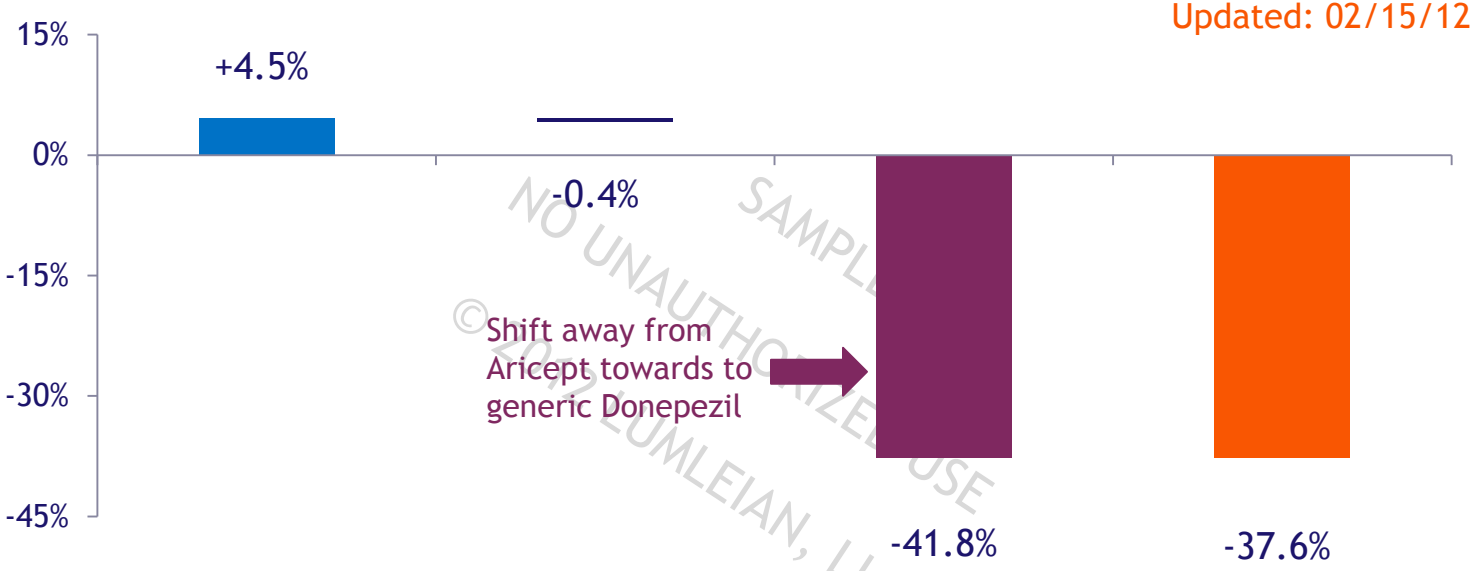
Notes: These forecasts are not representative of Lumleian's viewpoint; Ad-hoc Lumleian develops its own forecasts for clients based on its proprietary analytics and research; Pipeline includes: Bapineuzumab ('13), Gammagard ('12), Solanezumab ('13), PF-4494700 ('15), Vanutide Cridificar ('15)

Sources: Consensus estimates based on publicly available equity research forecasts that have been updated in the past 12 months (since 02/15/11); Consensus estimate is the 'straight line' average with each bank's forecast weighted equally

In Q4 ’11 US AD retail revenue fell ~37.6% driven by a ~41.8% decline in product mix, due to the large shift to generic donepezil; Days of therapy grew ~4.5% in parallel with total prescription volume.

## Decomposition of Q4’11 US Alzheimer's Retail Revenue Growth (over Q4 ’10)

Updated: 02/15/12






| | Days of Therapy | Price per day (Independent of Mix) | Product Mix | Retail Revenue |
|---|---|---|---|---|
| YTD 2011 vs. 2010 | 3.9% | 6.1% | -31.2% | -21.2% |

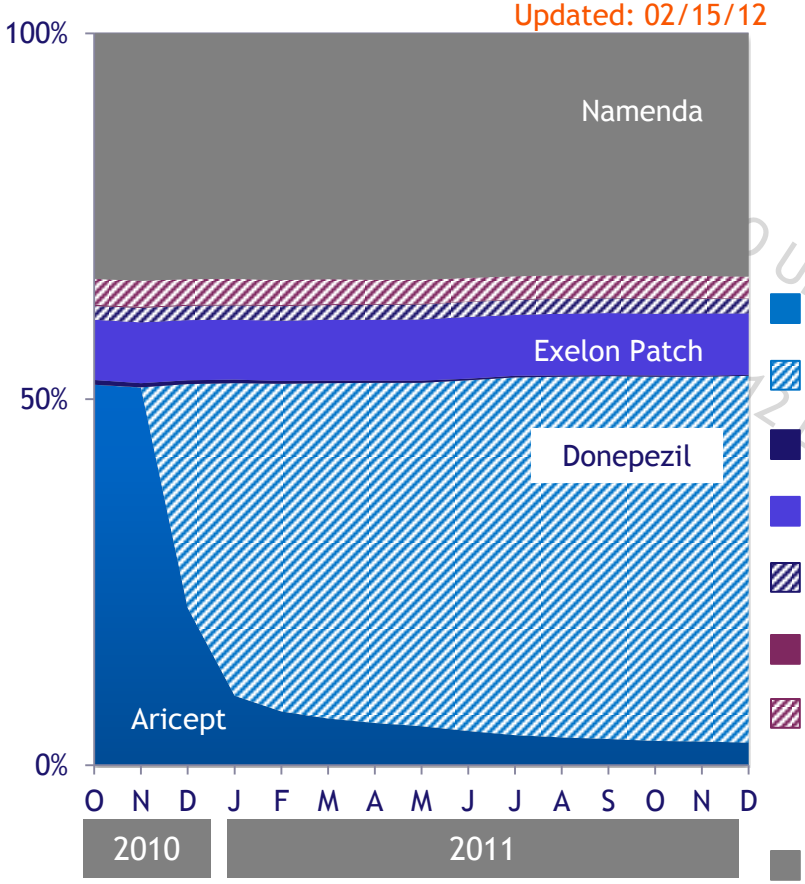
Notes: Revenues include both branded and generic products; YTD growth compares 2011 vs. 2010; QTD growth compares the 3 months 10/11-12/11 vs. the 3 months 7/11-9/11

Sources: SDI (IMS) retail sales and prescription data

# In the US generics now command ~55% share of total prescription volume; More than 90% of Aricept Rx has shifted to generic donepezil since November 2010; Namenda and Exelon patch, respectively maintain relatively stagnant ~33% and ~8.5% shares.

US Alzheimer's Prescription Share (TRx)

Updated: 02/15/12




| | Share | Share Change (% points) | | | CAGR | |
|---|---|---|---|---|---|---|
| | Dec-11 | 1MR | 3MR | 12MR | QTD | YTD |
| Total TRx | | | | | 0.2% | 0.4% |
| AChE Inhibitor | 66.8% | 0.3 | 0.5 | 0.0 | 0.9% | 0.4% |
| Aricept | 3.1% | -18.4 | -38.4 | -44.6 | -92.3% | -89.9% |
| Donepezil | 50.1% | 19.6 | 39.6 | 45.1 | 386.8% | 1765.4% |
| Exelon | 0.1% | -0.4 | -0.4 | -1.5 | -74.4% | -86.0% |
| Exelon Patch | 8.4% | 0.2 | 0.2 | 0.4 | 2.4% | 4.8% |
| Rivastigmine | 2.0% | 0.0 | 0.1 | 1.2 | 3.7% | 134.3% |
| Razadyne | 0.1% | -0.1 | -0.1 | -0.1 | -52.4% | -56.2% |
| Galantamine | 3.0% | -0.5 | -0.5 | -0.4 | -14.5% | -9.7% |
| NMDA Antagonist | 33.2% | -0.3 | -0.5 | 0.0 | -1.2% | 0.5% |
| Namenda | 33.2% | -0.3 | -0.5 | 0.0 | -1.2% | 0.5% |



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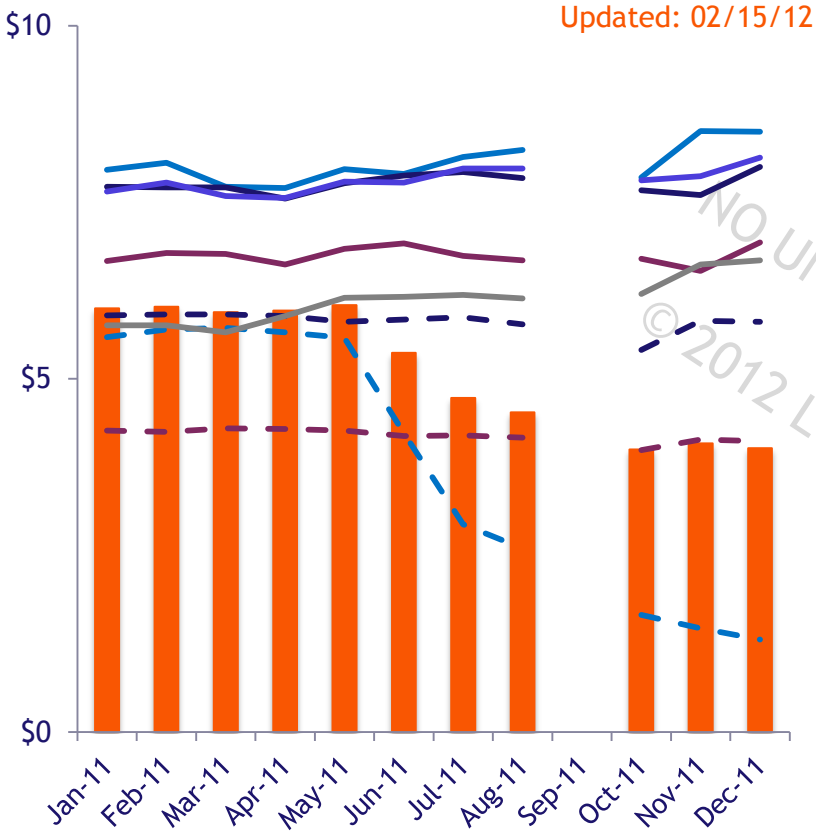
Notes: Prescription includes both branded and generic products; Share Change compares the share for 12/11 vs. 1 month, 3 months, and 12 months ago; YTD growth compares TRx for 2011 vs. the TRx for 2010; QTD growth compares TRx for the 3months 10/11-12/11 vs. the 3 months 10/10-12/10; MTD compares TRx for the month 12/11 vs. the month 12/10;
Sources: SDI (IMS) retail sales and prescription data

The average cost per a day of therapy is $4.02 and decreased by ~40% in 2011; The cost per day of therapy with Donepezil declined by ~77.5% in 2011 and the cost per day of therapy with Exelon patch and Namenda increased by ~9% and ~15% respectively.

## US Alzheimer Cost per Day of Therapy






| | Cost per Day | Change in Cost per Day | |
|---|---|---|---|
| | Dec-11 | 1 month (vs. Nov-11) | 12 month (vs. Dec-10) |
| Average TRx | $4.02 | -1.7% | -36.9% |
| **AChE Inhibitor** | | | |
| Aricept | $8.50 | -0.1% | 6.3% |
| Donepezil | $1.31 | -10.9% | -77.5% |
| Exelon | $8.00 | 5.3% | 3.0% |
| Exelon Patch | $8.13 | 3.3% | 9.1% |
| Rivastigmine | $5.81 | -0.2% | -2.2% |
| Razadyne | $6.93 | 6.1% | 6.0% |
| Galantamine | $4.12 | -0.5% | -4.6% |
| **NMDA Antagonist** | | | |
| Namenda | $6.68 | 0.9% | 15.2% |

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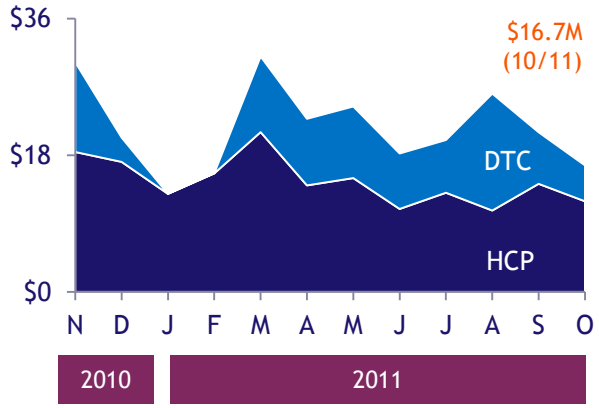
Notes: Prescription includes both branded and generic products; Cost change compares the price change for 12/11 vs. 1 month and 12 months ago; Data for the month of September was excluded as it had a high degree of variation vs. historic norms

Sources: SDI (IMS) retail sales and prescription data

# In the three months ending October '11 total promotional spend grew ~1.8%; Healthcare professional spend fell ~5.4% as Aricept and Namenda reduced sales forces in line with Aricept loosing exclusivity; Aricept substantially increased DTC investment for its 23mg formulation.

## Total Promotional Spend ($M)

Updated: 02/15/12

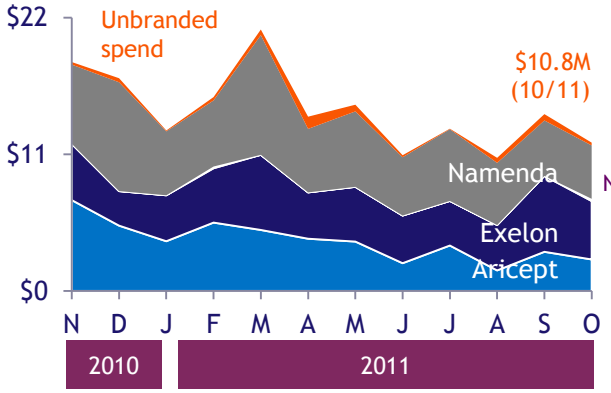



| | Share of Wallet | CAGR |
|---|---|---|
| | Oct-11 | 3MR |
| DTC | 28.4% | 13.7% |
| HCP | 71.6% | -5.4% |

- $~16.7M was spent on total promotion in October, a ~1.8% increase (3 month rolling), with ~71.6% of the expenditure focused on health care professionals
  - Exelon HCP spend increased ~22.3% in and decreased DTC spend, in light of Aricept LoE
  - Namenda accounted for ~36% of HCP spend and had no DTC spend
  - Aricept accounted for ~21.2% of HCP spend; Aricept launched a DTC campaign in August '11, focusing on its 23mg formulation

## Healthcare Professional Spend ($M)

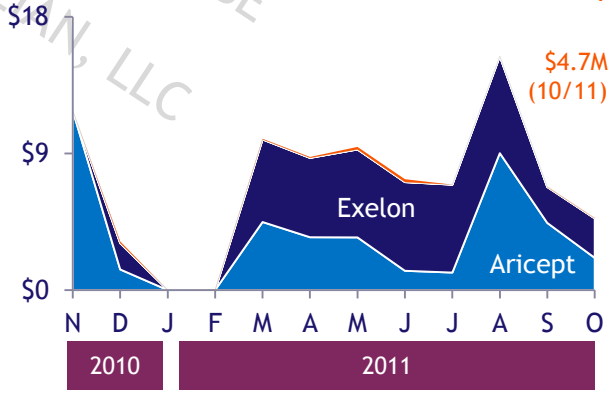
Updated: 02/15/12




| | Share of Voice | CAGR |
|---|---|---|
| | Oct-11 | 3MR |
| Namenda | 36.0% | -16.8% |
| Exelon | 39.4% | 22.3% |
| Aricept | 21.2% | -25.6% |

## Direct to Consumer Spend ($M)

Updated: 02/15/12




| | Share of Voice | CAGR |
|---|---|---|
| | Oct-11 | 3MR |
| Aricept | 44.9% | 164.2% |
| Exelon | 55.1% | -34.9% |



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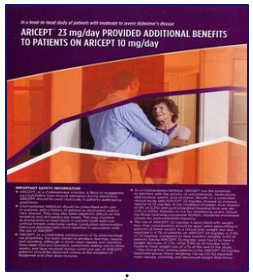
Note: Healthcare Professional (HCP) spend includes marketing to physicians, nurse practitioners, physician assistants through marketing & event promotions, journals, and online promotions; Direct to Consumer (DTC) includes marketing channels in television, radio, newspapers, magazines, outdoor advertisements, and internet; 3 month rolling (3MR) compares spend for the 3 months 8/11-10/11 vs. the 3 months 5/11-7/11

Sources: SDI (IMS) Promotion Audits, Kantar Media Research 2010 - 2011

Since August '11, Aricept promotional spend has shifted towards DTC for its 23mg formulation; Messaging has focused on increasing caregiver awareness; Meanwhile, generic manufacturers have emphasized their availability to physicians.

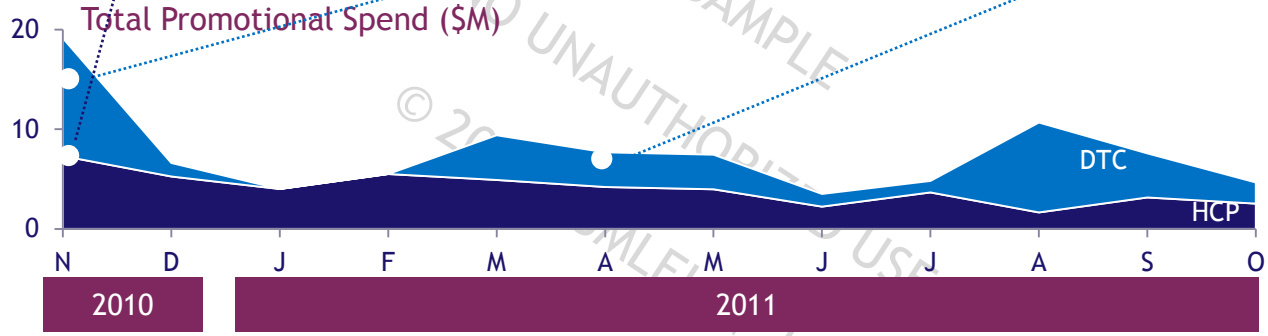
Aricept donepezil HCl tablet 5 mg, 10 mg and 23 mg




HCP
The head-to-head study results are in... Aricept 23 mg

DTC
"I want to give to the woman who always gave to me." Aricept 23 mg

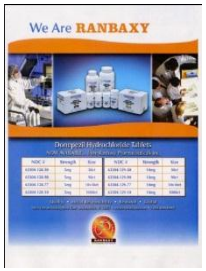
DTC
"I want to give to the woman who taught me to savor every moment." Aricept 23 mg.



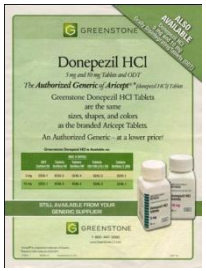

| | $4.7M (Oct-11) | CAGR 3MR |
|---|---|---|
| HCP | $2.5M | -25.6% |
| DTC | $2.1M | 164.2% |

| Share of voice | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HCP | 39.7% | 30.7% | 31.0% | 35.2% | 23.3% | 30.0% | 26.5% | 20.4% | 28.0% | 15.4% | 22.1% | 21.2% |
| DTC | 100.0% | 42.4% | 0.0% | 0.0% | 45.0% | 39.7% | 36.8% | 17.4% | 16.6% | 58.6% | 65.2% | 44.9% |

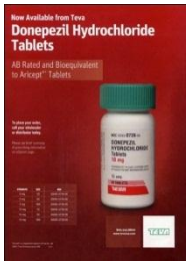
Generic Donepezil Penetration




02/11
*Ranbaxy*
We are Ranbaxy. Donepezil Hydrochloride Tablets. Now available. DONEPEZIL




01/11 & 06/11
*Greenstone*
Donepezil HCL 5mg and 10mg Tablets and ODT. The authorized generic of Aricept tablets. DONEPEZIL




07/11
*Teva*
Now available from Teva. Donepezil hydrochloride tablets. AB rated and Bioequivalent to Aricept tablets. DONEPEZIL

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Notes: Updated: 02/15/12
Sources: SDI Promotion Audits, Kantar Media Research

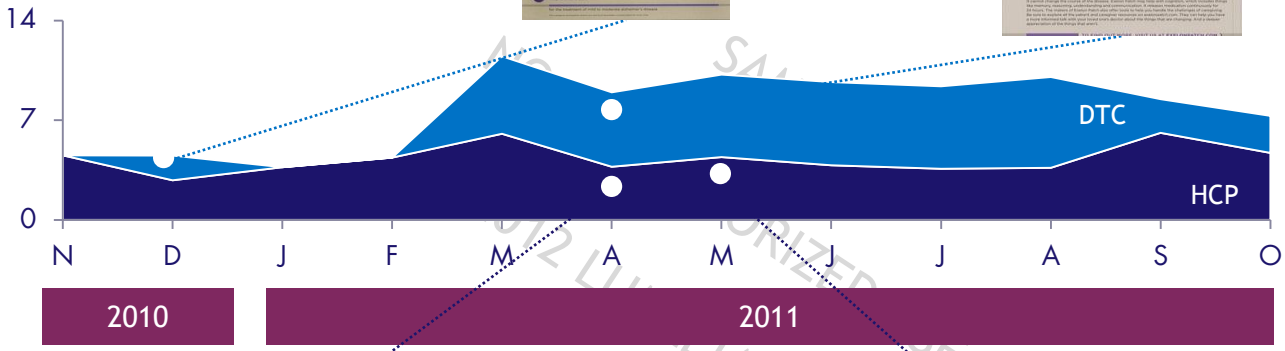
# Exelon increased promotional spend since March '11, in light of Aricept loss of exclusivity; Messaging has focused on the benefits of the patch formulation for both the caregiver and the patient.

EXELON (rivastigmine tartrate)

DTC
How is your loved one doing? How are you doing? EXELON PATCH


DTC
Throughout my life, mom has always been there for me. Now it's my turn. EXELON PATCH

Total Promotional Spend ($M)




| | $7.3M (Oct-11) | CAGR (QTD) |
|---|---|---|
| HCP | $4.7M | 22.3% |
| DTC | $2.6M | -34.9% |

| Share of voice | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HCP | 24.6% | 16.2% | 28.6% | 28.0% | 28.7% | 26.6% | 29.4% | 35.1% | 27.5% | 34.1% | 42.9% | 39.4% |
| DTC | 0.0% | 54.2% | 0.0% | 0.0% | 54.6% | 59.6% | 61.4% | 80.0% | 83.4% | 41.4% | 34.8% | 55.1% |


HCP
He gave it his all. You can help him. Exelon Patch is the only therapy indicated for both mild to moderate Alzheimer's dementia and mild to moderate Parkinson's disease dementia. EXELON PATCH


HCP
See what happen when you make the patch part of the equation. EXELON PATCH

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Notes: Updated: 02/15/12
Sources: SDI Promotion Audits, Kantar Media Research

# Q3 Namenda spend decreased ~4%; As a combination agent, Namenda invests only in DTP and maintains a ~35-45% share of voice; Messaging has focused on health plan coverage and the moderate/severe patient segment, where Exelon is not indicated.

Namenda memantine HCl


For patients with moderate to severe Alzheimer's disease, treat today with Namenda.

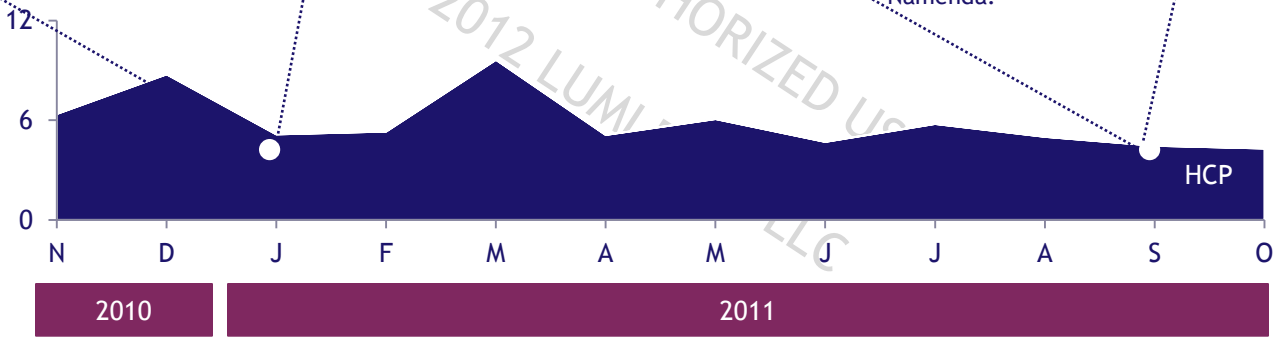

At the first sign of moderate Alzheimer's disease, treat today with Namenda. NAMENDA


Available on over 90% of Commercial Health Plan and Medicare Part D formularies. When it's moderate to severe Alzheimer's disease, treat today with Namenda.


Available on over 90% of commercial health plan and Medicare Part D formularies. For patients with moderate to severe Alzheimer's disease, treat today with Namenda. NAMENDA



Total Promotional Spend ($M)




| | $4.3M (Oct-11) | CAGR 3MR |
|---|---|---|
| HCP | $4.3M | -16.8% |

Share of voice

| | N | D | J | F | M | A | M | J | J | A | S | O |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HCP | 34.6% | 51.2% | 39.8% | 34.1% | 45.8% | 36.5% | 40.5% | 43.0% | 44.2% | 46.7% | 31.3% | 36.0% |
| DTC | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |

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Notes: Updated: 02/15/12

Sources: SDI Promotion Audits, Kantar Media Research

# Table of Contents





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# Table of Acronyms (1 of 2)

| | |
|---|---|
| 11A | 2011 Actual |
| 11F | 2011 Forecast |
| AB | Beta Amyloid |
| ABT | Abbott |
| AChE | Acetylcholinesterase |
| AD | Alzheimer's Disease |
| ADAMS | Aging, Demographics, and Memory Study |
| ADAS | Alzheimer's Disease Assessment Scale |
| ADCS-ADL | Alzheimer's Disease Cooperative Study - Activities of Daily Living |
| ADCS-CGIC | Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change |
| ApoE | Apolipoprotein E |
| ApoE4 | Apolipoprotein E-ε4 |
| APP | Amyloid Precursor Protein |
| AZN | AstraZeneca |
| B | Billions |
| BAX | Baxter |
| BID | Bis in Die (Twice daily) |
| BMS | Bristol-Myers Squibb |
| BSI | Beta Secretase Inhibitor |
| CA | Completer Analysis |
| CAGR | Compound Annual Growth Rate |
| CDR | Clinical Dementia Rating |
| CDR-sb | Clinical Dementia Rating- Sum of Boxes |
| CIBIC | Clinician's Interview-Based Impression of Change |
| CIBIC+ | Clinician's Interview-Based Impression of Change – Plus Caregiver |
| CNS | Central Nervous System |
| CSF | Cerebrospinal Fluid |
| CT | X-ray Computed Tomography |
| DAD | Disability Assessment for Dementia |
| DTC | Direct to Consumer |
| ELN | Elan |
| EU | European Union |
| FDA | Food and Drug Administration |
| GE | General Electric |
| GI | Gastrointestinal |
| GSK | GlaxoSmithKline |
| HCP | Health Care Professional |
| IVIG | Intravenous Immunoglobulin |
| IR | Immediate Release |
| JNJ | Johnson and Johnson |
| JP | Japan |
| LLY | Eli Lilly |
| LoE | Loss of Exclusivity |
| M | Millions |
| mg | Milligrams |
| MITT | Modified Intention to Treat |
| MMSE | Mini Mental Status Exam |
| MoA | Mechanism of Action |
| MR | Months Rolling, e.g. 1, 3, 12 |
| MRI | Magnetic Resonance Imaging |
| MRK | Merck |
| MTD | Month to Date |
| MYGN | Myriad Genetics |
| N | Number |
| NFT | Neurofibrillary Tangle |
| NMDA | N-methyl-D-aspartate |
| NTB | Neuropsychological Test Battery |
| NVS | Novartis |
| ODT | Orally Disintegrating Tablet |
| PCP | Primary Care Physician |
| PET | Positron Emission Tomography |
| PFE | Pfizer |
| Ph. | Phase |
| Ph.D. | Doctor of Philosophy |
| PiB | Pittsburg Compound B |
| PRN | Pro re nata (As needed) |
| p-tau | Phosphorylated Tau |
| Q1 | First Quarter |
| Q2 | Second Quarter |



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# Table of Acronyms (2 of 2)

| | |
|---|---|
| Q3 | Third Quarter |
| Q4 | Fourth Quarter |
| QD | Quaque Die (Once Daily) |
| QTD | Quarter To Date |
| RAGE | Receptor for Advanced Glycation End products |
| ROI | Return on Investment |
| RW | Rest of World |
| Rx | Prescription |
| SIB | Severe Impairment Battery |
| SNY | Sanofi-Aventis |
| SOC | Standard of Care |
| SS | Statistically Significant |
| SSI | Statistically Significant Improvement |
| TRGT | Targacept |
| t-tau | Total TAU |
| TRx | Total Prescriptions |
| US | United States |
| WW | World Wide |
| XR | Extended Release |
| Yrs. | Years |
| YTD | Year to date |



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## As a leadership team, we designed Lumleian's business model based on our collective experience in: academic R&D, bio-pharmaceutical industry, equity research and strategy consulting …

- Frank Deane, Ph.D. is a Director of Decision Science and Founder of Lumleian. Frank has over ten years experience working with life science companies and concurrently holds an appointment in the department of strategy at the Carroll School of Management, Boston College, where he teaches 'Strategic Issues in Pharma and Bio-Tech,' to MBA students. Prior to founding Lumleian, Frank was a director with Leerink Swann and a case team leader with Bain, where he gained substantial operational experience growing and operating a diverse set of businesses. Frank entered consulting after spending three years in the bio-pharmaceutical industry with Eli Lilly, supporting portfolio optimization and business unit strategic planning. He began his career, as a quantitative risk analyst working at BlackRock. Frank earned a Ph.D. in econometrics from the Krannert School of Management at Purdue University, where his dissertation focused on applying game theory and statistical modeling to optimize pharmaceutical sales and marketing resources. Frank has a bachelor of arts in economics from Princeton University.

- Mark Hochstetler, MBA is a Director of Decision Science at Lumleian. Mark has over ten years experience working with life science companies. Prior to joining Lumleian, Mark served as the CFO at OPK Biotech, which focuses on developing oxygen therapeutics for the treatment of anemia, ischemia, and trauma. Before segueing to industry, Mark spent 5 years as a strategy consultant and equity research analyst at Leerink Swann, where he covered: Array, Arqule, Ariad, Celgene, Chelsea, Cougar, Cubist, Genentech, GTx, Hana, Idenix, InterMune, Kosan, Millennium, MGI Pharma, Onyx, Poniard and Vertex. Mark earned an MBA from Duke University's Fuqua School of Business with a concentration in health sector management. Mark has a bachelor of arts in political science from Stanford University.

- Sarah Haigh Molina, Ph.D. is a Manager of Decision Science at Lumleian, where she leads the Academia and Non-profit practice. Sarah has over ten years experience working and researching in the life sciences. Prior to joining Lumleian, Sarah was an Assistant Professor of Medicine at Boston University School of Medicine where she served as the Director of High-throughput Screening. Before returning to academia, Sarah was US Operations Manager at Molecular Cytomics. Sarah earned a Ph.D. in biology from York University, an MBA from Boston University with a concentration in entrepreneurship, and a bachelors of science in biochemistry from Dundee University.

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## … Having lived the client experience, we know quality is paramount, and pioneered our approach with quality and process efficiency as dual mantras.

- Jean Kung, M.Eng, MBA as Manager of Process Efficiency and Quality Control oversees day-to-day operations and finances at Lumleian and has over five years experience working in the life sciences. Jean designed the process by which Lumleian efficiently and effectively creates and quarterly updates its disease state primers and serves as the final point of quality control. Prior to joining Lumleian, Jean served as a contract project manager to various life science clients. Before entrepreneurship, Jean was a clinical research associate at Health Policy Associates and a researcher at the Harris Orthopedic Biomaterials and Biomechanics Laboratory, Massachusetts General Hospital. Jean earned a masters of science in biological engineering from Cornell University and an MBA in the Health Sector Management Program from Boston University with a concentration in operations and technology management. Jean has a bachelor of science in biological engineering, also from Cornell University.

- Morgen Caroll, MBA as Manager of the Customer Experience at Lumleian, aspires to provide Lumleian's clients with superior care and service based on their particular needs. Morgen brings over five years life science experience and has a background in Marketing, Sales, and Public Relations. Prior to joining Lumleian, Morgen worked at GlaxoSmithKline, with responsibility for the company's flagship cardiology and endocrinology products. At GlaxoSmithKline, Morgen was a primary care and specialty care sales representative while serving as a liaison between product management teams and field sales. As a representative, Morgen consistently ranked in the top 10% of GSK's sales force, despite working in an inner city territory with significant access challenges. Prior to entering the life sciences Morgen worked on the sales and marketing staff at Philadelphia Magazine and Food & Wine Magazine. Morgen earned an MBA from the Villanova School of Business with a concentration in marketing, and a bachelor of arts in English from Gettysburg College.

- Qingwei Sun, M.Eng, MS as a Decision Science Analyst oversees secondary data collection, synthesis and analysis and designed analytical methodologies fundamental to Lumleian's knowledge management platform. KM database. Using meta-analysis method, he aggregates the clinical and commercial data required to generate Lumleian's disease state primers. His work has wide application in product development, portfolio management, and investment strategy for both large pharmaceutical companies and emerging bio-techs. Qingwei, who is fluent in Chinese and Japanese, leads our work with Asian clients. Qingwei joined Lumleian after obtaining a Master of Science degree from Harvard School of Public Health. He earned both Bachelor and Master of Engineering degrees from Kyoto University, Japan, concentrating in materials science.



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