Will the Next Five Years Witness an Innovation Wave in Medicines for Alzheimer’s?

The Healthcare System Is Not Ready for New Alzheimer’s Drugs

Success in drug development for Alzheimer’s disease has been elusive. Recent analysis has shown a near 100% failure rate in the past decade. Yet, each failed trial advances the science and presents the opportunity to apply new insights. As a result, there are a significant number of compounds in Phase 3, the final stage of drug development. Seventeen drugs in this final stage are likely to finish testing and could be available to people with the disease in the next five years. These findings are based on the analysis led by ResearchersAgainstAlzheimer’s, a global network of leading Alzheimer’s researchers at top academic institutions and corporations.

Our analysis leads us to be cautiously optimistic that innovative treatments are within our reach.

We need to make sure the healthcare system is ready.

Understanding the Alzheimer’s Drug Development Pipeline

Robust Alzheimer’s Pipeline Offers Promise for Treatment – Despite Recent Track Record

MORE THAN A DECADE SINCE A NOVEL ALZHEIMER’S DRUG WAS APPROVED
Namenda was approved by the FDA in 2003, marking the last time a novel Alzheimer’s therapy reached the market.¹

PIPELINE OUTLOOK
There are approximately 50 drugs in Phase 2 trials and about a dozen drugs in Phase 2/3 trials.²

ROUTE OF ADMINISTRATION
Several of these new, innovative treatments will be administered by infusion — bringing new requirements for settings of care.

Phase 3 Drugs in Development That Could Launch in the Next Five Years

<table>
<thead>
<tr>
<th>Drug</th>
<th>Estimated Trial Completion</th>
<th>Estimated Regulatory Filing</th>
<th>Estimated Launch Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brexpiprazole</td>
<td>2016</td>
<td>2017</td>
<td>2018</td>
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<tr>
<td>Aripiprazole</td>
<td>2017</td>
<td>2018</td>
<td>2019</td>
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<tr>
<td>Solanezumab</td>
<td>2019</td>
<td>2020</td>
<td>2021</td>
</tr>
<tr>
<td>Masitinib</td>
<td>2016</td>
<td>2017</td>
<td>2018</td>
</tr>
<tr>
<td>TRx0237</td>
<td>2017</td>
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<tr>
<td>Idalopirdine</td>
<td>2016</td>
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<tr>
<td>Sodium Oligo</td>
<td>2017</td>
<td>2018</td>
<td>2019</td>
</tr>
<tr>
<td>Azeliragon</td>
<td>2016</td>
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<td>2018</td>
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<tr>
<td>Nivadipine</td>
<td>2017</td>
<td>2018</td>
<td>2019</td>
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<tr>
<td>ALZT-0P1</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
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<tr>
<td>APV-786</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
</tr>
<tr>
<td>ALZ-801</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
</tr>
<tr>
<td>Aducanumab</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
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KEY
- Red: Estimated Trial Completion
- Blue: Estimated Regulatory Filing
- Orange: Estimated Launch Date
Alzheimer’s is a Growing Threat Across the Globe

America’s Healthcare System Is Not Prepared for New Alzheimer’s Treatments

Methodology

This analysis was constructed through extensive research and interviews, including interviews with company executives about publicly available information, SEC filings, company reports, presentations at medical conferences and media coverage. Additionally, academic research experts and select ResearchersAgainstAlzheimer’s (RA2) members provided input and review of the analysis. However, the responsibility for the content of this report belongs solely to UsAgainstAlzheimer’s, the convener of RA2, and not to any other organization or individual. When complete information pertaining to compound development milestones was not available, the research team estimated the timing of milestones based on our experience in pharmaceutical drug development. Information presented in this analysis does not include drugs that are in Phase 2/3 or earlier clinical trials. This report focuses only on drugs in Phase 3 clinical trials. This information is subject to change given the nature of clinical trials and drug development. Our intention is to provide regular updates on the status of drug development in Alzheimer’s, and we welcome input and corrections.
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Route of Administration</th>
<th>MOA (Mechanism of Action)</th>
<th>Phase of Drug Development</th>
<th>Target Population</th>
<th>Length of Current Trial</th>
<th>Number of Trial Participants</th>
<th>Estimated Trial Completion</th>
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</tr>
</thead>
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<tr>
<td>Aducanumab</td>
<td>Biogen</td>
<td>Infusion</td>
<td>anti-Abeta mAb</td>
<td>Phase 3 (ENGAGE and EMERGE)</td>
<td>People with MCI due to Alzheimer’s disease or mild Alzheimer’s disease as ascertained by a positive amyloid PET scan (Trials 1 and 2)</td>
<td>18 months (Trials 1 and 2)</td>
<td>1,350 participants (Trials 1 and 2)</td>
<td>First half of 2019 (Trials 1 and 2)</td>
<td>Q1 2020</td>
<td>Q3 2020</td>
</tr>
<tr>
<td>ALZ-801</td>
<td>Alzheon</td>
<td>Oral</td>
<td>Oral inhibitor of amyloid aggregation and neurotoxicity</td>
<td>Phase 3</td>
<td>APOE4/4 homozygous Alzheimer’s patients</td>
<td>18 months</td>
<td>Unknown</td>
<td>Q1 2019</td>
<td>Q1 2020</td>
<td>Second half of 2020</td>
</tr>
<tr>
<td>ALZT-0P1</td>
<td>AZTherapies</td>
<td>Oral</td>
<td>The first drug inhibits beta-amyloid peptide polymerization and lowers cytokine production. The second inhibits the neuroinflammatory response.</td>
<td>Phase 3</td>
<td>Subjects with evidence of early Alzheimer’s disease</td>
<td>72 weeks</td>
<td>600 participants</td>
<td>March 2018 (Q1)</td>
<td>March 2019 (Q1)</td>
<td>Q4 2019</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Otsuka Pharmaceuticals</td>
<td>Oral</td>
<td>Dopamine partial agonist</td>
<td>Phase 3</td>
<td>Patients with agitation associated with dementia of the Alzheimer’s type</td>
<td>10 weeks</td>
<td>880 participants</td>
<td>July 2017 (Q3)</td>
<td>Late 2017</td>
<td>First half of 2018</td>
</tr>
<tr>
<td>AVP-786</td>
<td>Avanir Pharmaceuticals</td>
<td>Oral</td>
<td>Novel investigational drug product consisting of a combination of deuterium modified dextromethorphan and ultra-low dose quinidine, used as a metabolic inhibitor</td>
<td>Phase 3</td>
<td>Treatment of agitation in patients with dementia of the Alzheimer’s type (Trials 1,2,3)</td>
<td>12 weeks (Trials 1 and 2) 52 weeks (Trial 3)</td>
<td>380 participants (Trial 1) 325 participants (Trial 2) 550 participants (Trial 3)</td>
<td>July 2018 (Trials 1 and 2) July 2019 (Trial 3)</td>
<td>July 2019 (Q3)</td>
<td>Q1 2020</td>
</tr>
<tr>
<td>Azeliragon</td>
<td>vTv Therapeutics</td>
<td>Oral</td>
<td>RAGE antagonist</td>
<td>Phase 3</td>
<td>People with clinical diagnosis of mild probable Alzheimer’s disease. (Trials 1 and 2)</td>
<td>18 months (Trials 1 and 2)</td>
<td>400 participants (Trials 1 and 2)</td>
<td>Q4 2017 (sub-study A) (Trial 1) Q2 2018 (sub-study B) (Trial 2)</td>
<td>2018</td>
<td>Q2 2019</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Otsuka Pharmaceuticals</td>
<td>Oral</td>
<td>Dopamine receptor D2 partial agonist</td>
<td>Phase 3</td>
<td>Treatment of agitation in patients with Alzheimer’s dementia (Trials 1 and 2)</td>
<td>12 weeks (Trials 1 and 2)</td>
<td>420 participants (Trial 1) 230 participants (Trial 2)</td>
<td>June 2017 (Q2) (Trials 1 and 2)</td>
<td>December 2017 (Q4)</td>
<td>June 2018 (Q2)</td>
</tr>
<tr>
<td>Crenezumab</td>
<td>Hoffmann-La Roche</td>
<td>Infusion</td>
<td>Fully humanised, monoclonal antibody designed to target all forms of beta amyloid</td>
<td>Phase 3</td>
<td>People with prodromal to mild Alzheimer’s disease</td>
<td>100 weeks</td>
<td>750 participants</td>
<td>2021</td>
<td>July 2022 (Q3)</td>
<td>Q1 2023</td>
</tr>
</tbody>
</table>
### PIPELINE ANALYSIS (CONT.)

<table>
<thead>
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</tr>
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<tr>
<td>Gantenerumab</td>
<td>Hoffmann-La Roche</td>
<td>Infusion</td>
<td>IgG1 antibody designed to bind with subnanomolar affinity to a conformational epitope on Aβ fibrils.</td>
<td>Phase 3 (Trial 1)</td>
<td>24 weeks (Trials 1, 2, and 3)</td>
<td>930 participants</td>
<td>October 2016 (Q4)</td>
<td>September/October 2017</td>
<td>Q4 2018</td>
</tr>
<tr>
<td>Idalopirdine</td>
<td>H. Lundbeck</td>
<td>Oral</td>
<td>Serotonin 6 (5-HT6) receptor antagonist</td>
<td>Phase 3</td>
<td>6 months</td>
<td>675 participants</td>
<td>April 2017 (Q2)</td>
<td>Q4 2017 if interim analysis is positive and approval granted by the authorities</td>
<td></td>
</tr>
<tr>
<td>Masitinib</td>
<td>AB Science</td>
<td>Oral</td>
<td>Targeting of Mast Cell through c-Kit inhibition</td>
<td>Phase 3</td>
<td>6 months</td>
<td>200 participants</td>
<td>August 2020 (Q3)</td>
<td>Q4 2020</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>National Institute on Aging, Johns Hopkins Bloomberg School of Public Health</td>
<td>Oral</td>
<td>Inhibits the reuptake of dopamine and norepinephrine</td>
<td>Phase 3</td>
<td>18 months</td>
<td>500 participants</td>
<td>December 2017 (Q4)</td>
<td>Q3 2019</td>
<td></td>
</tr>
<tr>
<td>Nilvadipine</td>
<td>Astellas Pharma and Archer Pharmaceuticals, Inc.</td>
<td>Oral</td>
<td>Dihydropyridine calcium channel blocker</td>
<td>Phase 3</td>
<td>24 weeks</td>
<td>1,150 participants</td>
<td>Second half of 2017</td>
<td>Second half of 2018</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Takeda Pharmaceutical Company, Zinfandel Pharmaceuticals</td>
<td>Oral</td>
<td>Insulin sensitizer of the thiazolidinedione class of peroxisome-proliferator activated receptor γ (PPARγ) agonists.</td>
<td>Phase 3</td>
<td>5 years (Trial 1)</td>
<td>3,500 participants</td>
<td>July 2019 (Q3)</td>
<td>Q1 2021</td>
<td></td>
</tr>
<tr>
<td>RVT-101</td>
<td>Akovant</td>
<td>Oral</td>
<td>5HT-6 antagonist</td>
<td>Phase 3</td>
<td>24 weeks</td>
<td>1,150 participants</td>
<td>Second half of 2017</td>
<td>Second half of 2018</td>
<td>Q1 2019</td>
</tr>
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<tr>
<td><strong>Sodium Oligo-mannurrate</strong></td>
<td>Shanghai Greenvalley Pharmaceutical Co.</td>
<td>Unknown</td>
<td>Oligosaccharide that binds to more than one region of amyloid-β (Aβ) and enhances clearance of the protein from the brain</td>
<td>Phase 3</td>
<td>Patients with mild to moderate Alzheimer’s disease</td>
<td>36 weeks</td>
<td>788 participants</td>
<td>May 2017 (Q2)</td>
<td>May 2018 (Q2)</td>
</tr>
<tr>
<td><strong>Solanezumab</strong></td>
<td>Eli Lilly</td>
<td>Infusion</td>
<td>Monoclonal antibody that binds to soluble monomeric forms of amyloid-beta</td>
<td>Phase 3 (EXPEDITION 3) (Trial 1) Phase 3 (EXPEDITION EXT) (Trial 2) Phase 2 (DIAN-TU) (Trial 3) Phase 3 (A4) (Trial 4)</td>
<td>Participants with mild Alzheimer’s disease. (Trial 1) Patients with Alzheimer’s disease. (Trial 2) People with an inherited autosomal-dominant mutation in APP, presenilin-1, or presenilin-2. (Trial 3) People who may be at risk for memory loss and cognitive decline due to Alzheimer’s disease. (Trial 4)</td>
<td>80 weeks. (Trial 1) 400 mg administered once every 4 weeks by intravenous infusion (IV) for 100 weeks. (Trial 2) Phase 1: 2 years Phase 2: 3 years. (Trial 3) 400 mg solanezumab intravenously every 4 weeks for 168 weeks. (Trial 4)</td>
<td>2,100 participants (Trial 1) 1,275 participants (Trial 2) 210 participants (Trial 3) 1,150 participants (Trial 4)</td>
<td>October 2016 (Q4) (Estimated primary completion date) (Trial 1) November 2018 (Q4) (Trial 2) December 2019 (Q4) (Trial 3) April 2020 (Q2) (Trial 4)</td>
<td>October 2017 (Q4)</td>
</tr>
<tr>
<td><strong>TRx0237</strong></td>
<td>TauRx Therapeutics</td>
<td>Oral</td>
<td>Second-generation tau protein aggregation inhibitor.</td>
<td>Phase 3</td>
<td>Patients with mild Alzheimer’s disease with a CDR score of 0.5 or 1 and an MMSE of 20–26 (inclusive). (Trial 1) Patients with mild to moderate Alzheimer’s disease with a CDR score of 1 to 2 and an MMSE of 14–26 (inclusive). (Trial 2) Patients with probable bvFTD who have frontotemporal atrophy confirmed by MRI and whose MMSE is 20 or higher. (Trial 3) Subjects completing Phase 3 studies above with Alzheimer’s disease or Behavioral Variant Frontotemporal Dementia (bvFTD). (Trial 4)</td>
<td>18 months (Trial 1) 15 months (Trial 2) 12 months (Trial 3) 29 months (Trial 4)</td>
<td>800 participants (Trial 1) 890 participants (Trial 2) 220 participants (Trial 3) 1,300 participants (Trial 4)</td>
<td>August 2016 (Q3) (Trial 1) March 2016 (Q1) (Trial 2) April 2016 (Q2) (Trial 3) January 2017 (Q1) (Open-Label Extension Study) (Trial 4)</td>
<td></td>
</tr>
<tr>
<td><strong>Verubecestat</strong></td>
<td>Merck</td>
<td>Oral</td>
<td>Small-molecule inhibitor of BACE1 and BACE2</td>
<td>Phase 3</td>
<td>Participants with prodromal Alzheimer’s disease. (Trial 1) Participants with mild to moderate Alzheimer’s disease. (Trial 2)</td>
<td>104 weeks (Trial 1) 78 weeks (Trial 2)</td>
<td>1,500 participants (Trial 1) 1,960 participants (Trial 2)</td>
<td>July 2019 (Q3), primary completion date. (Trial 1) July 2017 (Q3), primary completion date. (Trial 2)</td>
<td>July 2020 (Q3)</td>
</tr>
</tbody>
</table>

Based on expert interviews, Agenebio’s Levetiracetam could shortly enter Phase 3 clinical trials.
RA2 PIPELINE END NOTES

Aducanumab
- ResearchersAgainstAlzheimer’s Analysis

ALZ-801
- ResearchersAgainstAlzheimer’s Analysis

ALTZ-OP1
- ResearchersAgainstAlzheimer’s Analysis

Aripiprazole
- "Aripiprazole for the Treatment of Patients With Agitation Associated With Dementia of the Alzheimer’s Type.” ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show?term=aripiprazole+alzheimer%75rank=2
- Company Interview

AVP-786
- ResearchersAgainstAlzheimer’s Analysis

Azeliragon
- ResearchersAgainstAlzheimer’s Analysis

Brexpiprazole

Crenuzumab
- Company Interview
- "CREAD Study: A Study of Crenuzumab Versus Placebo to Evaluate the Efficacy and Safety in Participants With Mild to Moderate Alzheimer’s Disease (AD).” ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT02670083
- ResearchersAgainstAlzheimer’s Analysis

Gantenerumab
- Company Interview
- "Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Poten-tial Disease Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer’s Disease Caused by a Genetic Mutation. (DIAN-TU).” ClinicalTrials.gov. https://www.clinicaltrials.gov/show/NCT01760005
- ResearchersAgainstAlzheimer’s Analysis

Glatiramer acetate

Masitinib
  “A Phase 3 Study to Evaluate the Safety and Efficacy of Masitinib in Patients With Mild to Moderate Alzheimer’s Disease.” ClinicalTrials.gov. https://www.clinicaltrials.gov/show/NCT01872598
- Company Interview
- ResearchersAgainstAlzheimer’s Analysis

Methylphenidate
- "Apathy in Dementia Methylphenidate Trial 2 (ADMET2).” ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show?term=apathy-in-dementia%75rank=2&OpenType¼InitPhrase%75&rank=43
- ResearchersAgainstAlzheimer’s Analysis

Nilvadipine
- Company Interview
- ResearchersAgainstAlzheimer’s Analysis

Pioglitazone
- "Biomarker Qualification for Risk of Mild Cognitive Impairment (MCI) Due to Alzheimer’s Disease (AD) and Safety and Efficacy Evaluation of Pioglitazone in Delaying Its Onset (TOMMORROW).” ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT01931567?term=pioglitazone%2C+alzheimer%2C+rank=1
- Company Interview
- ResearchersAgainstAlzheimer’s Analysis
ResearchersAgainstAlzheimer’s (RA2) is a network of more than 400 Alzheimer’s researchers established by UsAgainstAlzheimer’s to advocate for federal research funding and policy reform in order to stop Alzheimer’s disease. RA2 believes that an effective treatment for Alzheimer’s is within reach if governments, industry, and citizens are willing to commit the resources and institute the policy changes that are necessary.

UsAgainstAlzheimer’s (US2A) is an innovative non-profit organization demanding — and delivering — a solution to Alzheimer’s. Driven by the suffering of millions of families, UsAgainstAlzheimer’s presses for greater urgency from government, industry and the scientific community in the quest for an Alzheimer’s cure — accomplishing this through effective leadership, collaborative advocacy, and strategic investments.

Our intention is to provide regular updates on the status of drug development in Alzheimer’s, and we welcome input and corrections.

Contact: ymiller@highlanterngroup.com

Released March 2016

RVT-101
- ResearchersAgainstAlzheimer’s Analysis

Verubecestat
- Company Interview
- ResearchersAgainstAlzheimer’s Analysis

Footnotes
2. “There are approximately 50 drugs in Phase 2 trials and about a dozen drugs in Phase 2/3 trials.” AlzForum. http://www.alzforum.org/therapeutics

ResearchersAgainstAlzheimer’s would like to thank Dr. David Morgan, CEO of the University of South Florida’s Health Byrd Alzheimer’s Institute; Dr. Jeffrey Cummings, Director of the Cleveland Clinic Lou Ruvo Center for Brain Health; Dr. Reisa Sperling, Director, Center for Alzheimer Research and Treatment at Brigham and Women’s Hospital, Harvard Medical School; and Dr. Rachelle Duddy, Director of the Alzheimer’s Disease and Memory Disorders Center at Baylor College of Medicine for reviewing this pipeline. Their insight and feedback was invaluable.

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