Supplementary Material

Alzheimer's Disease: Key Insights from Two Decades of Clinical Trial Failures

Supplementary Table 1. Details of the 40 unique phase 3 compound failures from 2004 to the present.

Failure Year	Clinical Trial #	Ph	Target AD Patients	Clinical Trial Design	Primary Clinical Endpoint	Biomarker: Inclusion / Exclusion Criteria	Biomarker: Efficacy Evaluation	Results and Notes	Main Sponsor
2020. **Solanezumab** (LY2062430). **Aβ plaque formation** - immunotherapy to remove soluble Aβ									
	NCT04623242	II/III	familial AD	194 pts, 18-80 y, >208 wk, 4 arms (includes gantenerumab arms)	DIAN-MCE ^	genetic, MRI	MRI, PET (Aβ, tau, glucose), CSF (Aβ, tau, NfL), plasma (Aβ, NfL)	no significant efficacy [1]	Washington Univ. School of Medicine
	NCT00905372	III	mild-moderate	1,012 pts, 55+ y, 80 wk, 2 arms	ADAS-Cog, ADCS-ADL	MRI or CT	MRI, plasma (Aβ)	no significant efficacy [2, 3]	Eli Lilly
	NCT00904683	III	mild-moderate	1,040 pts, 55+ y, 80 wk, 2 arms	ADAS-Cog	MRI or CT	MRI, plasma (Aβ)	no significant efficacy [2, 3]	Eli Lilly
	NCT01900665	III	mild	2,129 pts, 55-90 y, 80 wk, 2 arms	ADAS-Cog	MRI or CT, PET (Aβ) or CSF (Aβ)	MRI, plasma (Aβ), PET (Aβ), CSF (Aβ)	trial terminated, no efficacy [4]	Eli Lilly
	NCT02760602	III	prodromal	26 pts (aiming for 2,450), 55-85 y, 24 mo, 2 arms	ADAS-Cog	MRI or CT, PET (Aβ) or CSF (Aβ)	MRI, PET (Aβ, tau), CSF (Aβ, tau), plasma (Aβ)	trial terminated, due to failure in other Ph III trials	Eli Lilly
2020. **Gantenerumab** (RO4909832, RG1450). **Aβ plaque clearance** - immunotherapy for aggregated Aβ peptides									
	NCT04623242	II/III	familial AD	194 pts, 18-80 y, >208 wk, 4 arms (includes solanezumab arms)	DIAN-MCE ^	genetic, MRI	MRI, PET (Aβ, tau, glucose), CSF (Aβ, tau, NfL), plasma (Aβ, NfL)	no significant efficacy [5]	Washington Univ. School of Medicine
	NCT01224106	III	prodromal	797 pts, 50-85 y, 104 wk, 5 arms	CDR-SB	none reported	CSF (Aβ, tau), MRI, *APOE*	trial terminated based on futility analysis, no significant efficacy [6]	Roche
2019. Elenbecestat (E2609). **Aβ production** - BACE inhibitor									
	NCT02956486	III	early (MCI-mild)	2,212 pts, 50-85 y, 24 mo, 3 arms	CDR-SB	PET (Aβ) or/and CSF (Aβ), MRI	PET (Aβ)	terminated early due to unfavorable risk/ benefit, discontinued [7, 8]	Eisai
2019. Crenezumab (MABT5102A, RG7412, RO5490245). **Aβ plaque formation** - targets soluble and possibly aggregated Aβ peptides									
	NCT02670083	III	prodromal-mild	813 pts, 50-85 y, 100 wk, 2 arms	CDR-SB	CSF (Aβ) or PET (Aβ), MRI	plasma (Aβ), MRI, genetic	terminated early based on futility analysis [9]	Roche
	NCT03114657	III	prodromal-mild	806 pts, 50-85 y, 100 wk, 2 arms	CDR-SB	CSF (Aβ) or PET (Aβ), MRI	plasma (Aβ), MRI, genetic	terminated early based on futility analysis [9]	Roche

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2019. Amilomotide (CAD106). **Aβ vaccine** – active immunotherapy to elicit antibody									
	NCT02565511	II/III	asymptomatic at-risk (*APOE* genotype) pts	480 pts, 60-75 y, 60-90 mo, 4 arms (includes umibecestat arms)	time to onset of MCI/ dementia due to AD, APCC	MRI, *APOE*	PET (Aβ, tau), CSF (Aβ, tau), serum (NfL), MRI	trial terminated based on futility analysis, program retired [10]	Novartis
2019. Umibecestat (CNP520). **Aβ production** - BACE inhibitor									
	NCT02565511	II/III	asymptomatic at-risk (*APOE* genotype) pts	480 pts, 60-75 y, 60-90 mo, 4 arms (includes amilomotide arms)	time to onset of MCI/ dementia due to AD, APCC	MRI, *APOE*	PET (Aβ, tau), CSF (Aβ, tau), serum (NfL), MRI	trial terminated based on futility analysis, worsening of cognition, discontinued [11]	Novartis
	NCT03131453	II/III	asymptomatic at-risk (*APOE* genotype) pts	1,145 pts, 60-75 y, 60-84 mo, 3 arms	time to onset of MCI / dementia due to AD, APCC	MRI, *APOE*	PET (Aβ, tau), CSF (Aβ, tau), serum (NfL), MRI	worsening of cognition, discontinued [11]	Novartis
2018. **Azeliragon** (TTP488, PF-04494700). **Inflammation** - RAGE antagonist									
	NCT02080364	III	mild	880 pts, 50+ y, 18 mo, 2 arms	ADAS-Cog, CDR-SB	MRI	MRI, PET (glucose)	no significant efficacy [12]	vTv
2018. **Atabecestat** (JNJ-54861911). **Aβ production** - BACE inhibitor									
	NCT02569398	II/III	asymptomatic Aβ positive at-risk (*APOE* genotype) pts	557 pts, 60-85 y, 54 mo, 3 arms	PACC *	*APOE*, CSF (Aβ) or PET (Aβ), MRI	none reported	trial terminated due to benefit/risk profile, no efficacy, liver toxicity, discontinued [13]	Janssen
2018. **Lanabecestat** (AZD3293, LY3314814). **Aβ production** - BACE inhibitor									
	NCT02245737	II/III	prodromal-mild	2,218 pts, 55-85 y, 104 wk, 3 arms	ADAS-Cog	PET (Aβ) or CSF (Aβ)	CSF (Aβ, tau), PET (Aβ, tau, glucose), MRI	trial terminated based on futility analysis, no significant efficacy, discontinued [14, 15]	AstraZeneca
	NCT02783573	III	mild	1,722 pts, 55-85 y, 78 wk, 4 arms	ADAS-Cog	none reported	CSF (Aβ, tau), PET (Aβ), MRI, rCBF	trial terminated based on futility analysis, no significant efficacy, discontinued [14, 15]	AstraZeneca
2018. **Verubecestat** (MK-8931). **Aβ production** - BACE inhibitor									
	NCT01739348	II/III	mild-moderate	1,958 pts, 55-85 y, 78 wk, 4 arms	ADAS-Cog, ADCS-ADL	MRI or CT	PET (Aβ), CSF (Aβ, tau), *APOE*	trial terminated based on futility analysis, no efficacy, adverse events [16-18]	Merck
	NCT01953601	III	prodromal	1,454 pts, 50-85 y, 104 wk, 3 arms	CDR-SB	PET (Aβ) or CSF (Aβ, tau), MRI or CT	MRI, PET (Aβ), CSF (Aβ, tau)	trial terminated based on futility analysis, some pts performed worse [18, 19]	Merck

Failure Year	Clinical Trial #	Ph	Target AD Patients	Clinical Trial Design	Primary Clinical Endpoint	Biomarker: Inclusion / Exclusion Criteria	Biomarker: Efficacy Evaluation	Results and Notes	Main Sponsor
2018. **Pioglitazone** (AD4833). **Energy utilization** - marketed diabetes medication and insulin sensitizer, binds PPARγ, possible anti-inflammatory effects									
	NCT01931566	III	asymptomatic at-risk pts	3,494 pts, 65-83 y, up to 5 y, 3 arms	time to MCI-AD ^^	genetic	*APOE*	trial terminated based on futility, lack of efficacy [20]	Takeda
2018. **Nilvadipine** (ARC029). **Vascular burden** - marketed calcium channel blocker to treat hypertension, increases cerebral blood flow									
	NCT02017340	III	mild-moderate	511 pts, 50+ y, 18 mo, 2 arms	ADAS-Cog	none reported	none reported in this study; discussions of various biomarkers in parallel study but no further details	no significant efficacy [21]	St. James's Hospital
2017. **Tricaprilin** (AC-1204). **Energy utilization** - induction of mild chronic ketosis to improve mitochondrial metabolism									
	NCT01741194	II/III	mild-moderate	418 pts, 66-90 y, 26 wk, 2 arms	ADAS-Cog	MRI or CT, *APOE*	none reported	no significant efficacy, failure due to new formulation [22]	Cerecin
2017. **Idalopirdine** (LY483518, SGS518, Lu AE58054). **Symptomatic** - 5-HT 6 receptor antagonist									
	NCT01955161	III	mild-moderate	933 pts, 50+ y, 24 wk, 3 arms	ADAS-Cog	none reported	none reported	no significant efficacy, discontinued [23, 23]	Lundbeck
	NCT02006641	III	mild-moderate	858 pts, 50+ y, 24 wk, 3 arms	ADAS-Cog	none reported	none reported	no significant efficacy, discontinued [23, 23]	Lundbeck
	NCT02006654	III	mild-moderate	734 pts, 50+ y, 24 wk, 2 arms	ADAS-Cog	none reported	none reported	no significant efficacy, discontinued [23, 23]	Lundbeck
2017. **Intepirdine** (RVT-101, SB 742457, GSK 742457). **Symptomatic** - 5-HT 6 receptor antagonist									
	NCT02585934	III	mild-moderate	1,315 pts, 50-85 y, 24 wk, 2 arms	ADAS-Cog, ADCS-ADL	none reported	none reported	no significant efficacy, discontinued [25, 26]	Axovant
2017. **SK-PC-B70M**. **Neuroprotectant / Antioxidant** – neuroprotective against cytotoxicity induced by $A\beta_{42}$, MOA not well defined									
	NCT01249196	III	mild-moderate	256 pts, 55-85 y, duration not stated, 4 arms	ADAS-Cog	MRI	none reported	discontinued [27]	SK Chemicals
2016. **TRx0237** (LMTM, LMT-X, Methylene Blue). **Tau** – inhibitor of tau aggregation or removal of existing aggregates									
	NCT01689246	III	mild-moderate	891 pts, <90 y, 15 mo, 3 arms	ADAS-Cog, ADCS-ADL	MRI	PET (glucose), MRI, CSF (Aβ, tau), *APOE*	no significant efficacy [28, 29]	TauRx
	NCT01689233	III	mild	800 pts, <90 y, 18 mo, 2 arms	ADAS-Cog, ADCS-ADL	MRI	MRI, PET (glucose), CSF (Aβ, tau), *APOE*	disputes about data presentation, but generally thought to have no significant efficacy [29]	TauRx
2015. **Encenicline** (EVP-6124, MT-4666). **Symptomatic** - partial selective agonist of nicotinic ACh receptor									
	NCT01969123	III	mild-moderate	474 pts, 55-85 y, 26 wk, 3 arms	ADAS-Cog, CDR-SB	MRI or CT	none reported	trial terminated, discontinued [30]	Forum

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	NCT01969136	III	mild-moderate	403 pts, 55-85 y, 26 wk, 3 arms	ADAS-Cog, CDR-SB	MRI or CT	none reported	trial terminated, discontinued [30]	Forum
2013. **Immunoglobulin** (IGIV). **Aβ plaque formation** - marketed for immune deficiencies, immunotherapy of polyclonal antibodies directed against Aβ									
	NCT00818662	III	mild-moderate	390 pts, 50-89 y, 18 mo, 4 arms	ADAS-Cog, ADCS-ADL	MRI or CT	MRI, plasma / serum (Aβ), CSF (Aβ, tau), PET (Aβ), *APOE*	no significant efficacy [31, 32]	Takeda
	NCT01524887	III	mild-moderate	508 pts, 50-89 y, 18 mo, 3 arms	ADAS-Cog, ADCS-ADL	MRI or CT	MRI	trial terminated due to other Ph 3 failure [32]	Takeda
2013. **Semagacestat** (LY450139). **Aβ production** - γ-secretase inhibitor									
	NCT00594568	III	mild-moderate	1,537 pts, 55+ y, 76 wk, 3 arms	ADAS-Cog, ADCS-ADL	MRI or CT	PET (glucose, Aβ), MRI, CSF (tau, Aβ), plasma (Aβ)	trial terminated, some pts performed worse, adverse events, discontinued [33, 34]	Eli Lilly
	NCT00762411	III	mild-moderate	1,111 pts, 55+ y, 76 wk, 2 arms	ADAS-Cog, ADCS-ADL	MRI or CT	PET (glucose, Aβ), MRI, CSF (tau, Aβ), plasma (Aβ)	discontinued [34]	Eli Lilly
2013. **Thalidomide**. **Inflammation** - marketed for immunological and inflammatory disorders and cancer, anti-inflammatory effect via TNFα									
	NCT01094340	II/III	mild-moderate	25 pts (185 pre-screened), 50-90 y, 24 wk, 2 arms	ADAS-Cog, CDR-SB, MMSE, ADCS-ADL	MRI or CT	CSF & blood mentioned, but no further details	no significant efficacy, poor tolerability [35]	Banner
2013. **Doxycycline, Rifampicin** (alone or in combination). **Inflammation** - marketed antibiotics, may decrease neuroinflammation, reduce amyloid and tau accumulation, reduce neurotoxicity									
	NCT00439166	III	mild-moderate	406 pts, 50+ y, 12 mo, 4 arms	ADAS-Cog, CDR-SB	none reported	CSF (tau, Aβ),	worsening of cognitive function [36]	Hamilton Health Sciences
2012. **Bapineuzumab** (AAB-001). **Aβ plaque formation** - immunotherapy for soluble Aβ peptides, and may clear Aβ plaques									
	NCT00575055	III	mild-moderate, *APOE* ε4 carriers	1,121 pts, 50-88 y, 18 mo, 3 arms	ADAS-Cog, DAD	MRI, *APOE*	PET (Aβ), CSF (tau), MRI	no significant efficacy, discontinued [37-39]	Janssen
	NCT00574132	III	mild-moderate, *APOE* ε4 non-carriers	1,331 pts, 50-88 y, 18 mo, 3 arms	ADAS-Cog, DAD	MRI, *APOE*	PET (Aβ), CSF (tau), MRI	no significant efficacy, discontinued [37-39]	Janssen
	NCT00676143	III	mild-moderate, *APOE* ε4 carriers	683 pts, 50-88 y, 18 mo, 3 arms	ADAS-Cog, DAD	MRI, *APOE*	PET (Aβ), CSF (tau), plasma (Aβ), MRI	trial terminated due other Ph 3 failures, discontinued [39, 40]	Pfizer
	NCT00667810	III	mild-moderate, *APOE* ε4 non-carriers	329 pts, 50-88 y, 18 mo, 3 arms	ADAS-Cog, DAD	MRI, *APOE*	PET (Aβ), CSF (tau), plasma (Aβ), MRI	trial terminated due other Ph 3 failures, discontinued [39, 40]	Pfizer
2012. **Ginkgo biloba**. **Neuroprotective / Antioxidant** - antioxidant activity by reducing oxidative damage									

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	NCT00010803	III	AD onset in normal-MCI pts	3,069 pts, 75+ y, 8 y, 2 arms	MMSE, CDR-SB, ADAS-Cog	none reported	*APOE*	no significant efficacy [41]	NCCIH
	NCT00276510	III/IV	AD onset in pts with memory complaints	2,878 pts, 70+ y, 5 y, 2 arms	MMSE, CDR-SB	none reported	none reported	no significant efficacy [42]	Ipsen
2011. **Rosiglitazone**. **Energy utilization** - marketed diabetes medication and insulin sensitizer, binds PPARγ, possible anti-inflammatory effects									
	NCT00428090	III	mild-moderate, based on *APOE* status	693 pts, 50-90 y, 24 wk, 8 arms	ADAS-Cog, CIBIC+	*APOE*	none reported	no significant efficacy, discontinued [43]	GSK
	NCT00348309	III	mild-moderate, based on *APOE* status	1,496 pts, 50-90 y, 54 wk 6 arms	ADAS-Cog, CDR-SB	CT or MRI, *APOE*	none reported	no significant efficacy, discontinued [44]	GSK
	NCT00348140	III	mild-moderate, based on *APOE* status	1,468 pts, 50-90 y, 54 wk, 6 arms	ADAS-Cog, CDR-SB	CT or MRI, *APOE*	none reported	no significant efficacy, discontinued [44]	GSK
2011. **Simvastatin**. **Cholesterol** - marketed lipid-lowering drug for hypercholesterolemia									
	NCT00053599	III	mild-moderate	406 pts, 50+ y, 18 mo, 2 arms	ADAS-Cog	none reported	none reported	no significant efficacy [45]	
2011. **Estrogen** (with/without **Progesterone**). **Hormone treatment** - female sex hormone replacement									
	NCT00066157	II/III	mild-moderate	43 female pts, 55-90 y, 15 mo, 4 arms, with/without progesterone	SRT, Stroop, CIBIC	none reported	none reported	weak efficacy reported, but no follow-up [46, 47]	Univ. of Wisconsin
	NCT00000176	III	AD	pt number not stated, 3 y, 65+ y, 3 arms, with/without progesterone	not stated	none reported	none reported	no follow-up report [47]	NIA
2010. **Latrepirdine** (Dimebolin, Pf-01913539). **Symptomatic** - marketed antihistamine to treat allergic rhinitis, may work via histamine H1 receptor blockage, other neurotransmitters, or calcium channels									
	NCT00675623	III	mild-moderate	598 pts, 50+ y, 6 mo, 3 arms	ADAS-Cog, CIBIC+	MRI or CT	none reported	no significant efficacy, discontinued [48, 49]	Medivation
	NCT00829374	III	mild-moderate	1,003 pts, 50+ y, 12 mo, 3 arms	ADCS-ADL, ADAS-Cog	MRI or CT	none reported	no significant efficacy, discontinued [49]	Medivation
	NCT00912288	III	moderate-severe	86 pts, 50+ y, 26 wk, 2 arms	SIB, ADCS-ADL	none reported	none reported	trial terminated due to earlier Ph 3 failure, discontinued [49]	Pfizer
	NCT00954590	III	moderate-severe	89 pts, 50+ y, 26 wk, 2 arms	ADCS-ADL, NPI	none reported	none reported	trial terminated due to earlier Ph 3 failure, discontinued [49]	Medivation

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2009. **Xaliproden** (SR 57746A). **Symptomatic** - 5-HT 1A receptor antagonist									
	NCT00104013	III	mild-moderate	1,455 pts, 50+ y, 18 mo, 3 arms	ADAS-Cog, CDR-SB	none reported	none reported	potential worsening of cognition and function, discontinued [50, 51]	Sanofi
	NCT00103649	III	mild-moderate	1,306 pts, 50+ y, 18 mo, 3 arms	ADAS-Cog, CDR-SB	none reported	none reported	potential worsening of cognition and function, discontinued [50, 51]	Sanofi
2009. **Lecozotan** (SRA-333). **Symptomatic** - 5-HT 1A receptor selective antagonist									
Date is estimate	NCT00277810	II/III	mild-moderate	250 pts, 50+ y, 6 mo, 3 arms	cognitive & functional scales (no other details)	none reported	*APOE*	discontinued [53]	Pfizer
2009. **Atomoxetine** (ATX). **Symptomatic** - marketed for ADHD, selective NE reuptake inhibitor									
	NCT00191009	II/III	mild-moderate	92 pts, 55+ y, 6 mo, 2 arms	ADAS-Cog	none reported	none reported	no significant efficacy, discontinued [54, 55]	Eli Lilly
2009. **Tarenflurbil** (MPC-7869, r-flurbiprofen). **Aβ production** - R-enantiomer of marketed NSAID flurbiprofen, modulation of APP / γ-secretase interaction									
	NCT00105547	III	mild	1,684 pts, 55+ y, 18 mo, 2 arms	ADAS-Cog, ADCS-ADL	none reported	none reported	no significant efficacy, discontinued [56, 57]	Myrexis
	NCT00322036	III	mild	800 pts, 55+ y, 18 mo, 2 arms	did not specify	none reported	none reported	trial terminated due to other Ph 3 failure [57]	Myrexis
2008. **Atorvastatin**. **Cholesterol** - marketed statin for hypercholesterolemia.									
	NCT00151502	III	mild-moderate	640 pts, 50-90 y, 80 wk, 2 arms	ADAS-Cog, ADCS-CGIC	none reported	none reported	no significant efficacy [58]	Pfizer
2008. **Indomethacin**. **Inflammation** - marketed NSAID, reduces prostaglandin synthesis									
	NCT00432081	III	mild-moderate	51 pts (aimed for 160), 40-90 y, 12 mo, 2 arms	ADAS-Cog	none reported	none reported	no significant efficacy [59]	Radboud Univ.
2007. **Naproxen, Celecoxib** (separate arms). **Inflammation** - marketed NSAID, COX inhibitors, reduces prostaglandin synthesis									
	NCT00007189	III	AD onset in pts with family history of AD	2,528 pts, 70+ y, ~1.5+7 y follow-up, 3 arms	composite of cognitive function tests **	none reported	none reported	no significant efficacy, discontinued [60-62]	Seattle Institute for Biomedical and Clinical Research
2007. **Tramiprosate** (3APS, Alzhemed™, NC-531, homotaurine). **Aβ plaque formation** - variant of amino acid taurine, binds to Aβ									
	NCT00088673	III	mild-moderate	1,052 pts, 50+ y, 18 mo, 2 arms	ADAS-Cog, CDR-SB	none reported	MRI	no significant efficacy, discontinued [63, 64]	Bellus
	NCT00217763	III	mild-moderate	930 pts, 50+ y, 18 mo, 3 arms	not stated	none reported	none reported	discontinued [64]	Bellus
2006. Raloxifene. Hormone treatment - selective estrogen receptor modulator									
Date is estimate	NCT00065767	II/III	mild-moderate	20 female pts, 55-90 y, 5 mo, 2 arms	not stated	none reported	none reported	no follow-up report, although another	Univ. of Wisconsin

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								clinical trial reported no efficacy [65]	
2004. **Neramexane** (MRZ 2/579). **Symptomatic** - NMDA receptor antagonist, similar to memantine									
	NCT00090116	III	moderate-severe	415 pts, 50+ y, 24 wk, 2 arms	SIB, ADCS-ADL	none reported	none reported	little details reported, discontinued [66]	Forest

Reported year of compound failure is a "best estimate" based on the publicly available information, as at times sponsors delay reporting the trial failure or do not report it at all; the most recent failure year is reported. Compound name includes alternate names, if any, in brackets. MOA (mechanism of action) class and description are based on weight of the evidence, as in some cases the MOA is not well understood or multiple potential mechanisms were listed. For any discrepancies in clinical trial design details between Clinical-Trails.gov and published paper, the latter is cited. Biomarkers: Aβ includes its variants (e.g., $A\beta_{40}$, $A\beta_{42}$, ratios); tau can be total tau or P-tau; MRI can be for whole brain or specific regions (e.g., hippocampus, ventricles, cortical regions). ^^ Consists of 4 cognitive measures: Wechsler Memory Scale-Revised Logical Memory Delayed Recall Test, Wechsler Adult Intelligence Sale Digit Symbol Substitution Test (WAIS), International Shopping List Task (ISLT), Mini-Mental State Examination (MMSE). * Preclinical Alzheimer cognitive composite, comprised of 4 components: Selective Reminding, Delayed Paragraph Recall, WAIS and MMSE. ^ Measured by composite of several test batteries as well as ADCS-ADL. ** Composite of seven cognitive assessment tests.

5-HT, Serotonin; Aβ, amyloid-β, ACh, acetylcholine; ADAS-Cog, Alzheimer's Disease Assessment Scale - cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study - Activities of Daily Living inventory scale; ADHD, attention deficit hyperactivity disorder; APP, amyloid precursor protein; APCC, Alzheimer's Prevention Initiative Composite Cognitive test; *APOE*, Apolipoprotein E; BACE, β-secretase; CDR-SB, Clinical Dementia Rating Scale - sum of boxes; CIBIC+, Clinician's Interview-Based Impression Change – plus; COX, cyclooxygenase; CSF, cerebrospinal fluid; CT, computerized axial tomography; DAD, Disability Assessment for Dementia; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; mo, months; MRI, magnetic resonance imaging; NCCIH, National Center for Complementary and Integrative Health; NE, norepinephrine; NfL, neurofilament light chain; NIA, National Institute on Aging; NMDA, N-methyl-D-aspartate; NPI, Neuropsychiatric Inventory; NSAID, non-steroidal anti-inflammatory drug; PACC, Preclinical Alzheimer Cognitive Composite; PET, positron emission tomography; Ph, phase; PPAR, peroxisome-proliferator activated receptor; pts, patients; RAGE, receptor for advanced glycation endproducts; rCBF, regional cerebral blood flow; SIB, Severe Impairment Battery; SRT, Buschke Selective Reminding Test; Stroop, Stroop interference condition; TNF, tumor necrosis factor; WAIS, Wechsler Adult Intelligence Scale; wk, weeks; y, years

Supplementary Table 2. Details of the 58 unique phase 2 compound failures from 2004 to the present.

Failure Year	Compound	MOA Class	MOA Description	Clinical Trial #	Ph	Results and Notes	Main Sponsor
2021	**Gosuranemab** (BIIB092)	**Tau**	antibody against extracellular N-terminal fragments of tau	NCT03352557	II	discontinued [67]	Biogen
2021	**Tilavonemab** (ABBV-8E12, C2N 8E12, HJ9.3)	**Tau**	recognizes aggregated, extracellular form of pathological tau	NCT02880956	II	discontinued [68]	AbbVie
2021	**Zagotenemab** (LY3303560)	**Tau**	selectively binds to aggregates over monomer tau at its N-terminal region	NCT03518073	II	discontinued [69]	Eli Lilly
2019	**DCB-AD1**	**Other**	undefined MOA, potential scavenging activities, anti-inflammatory or anti-peroxidation actions	NCT00154635	II	discontinued [70]	National Taiwan Univ. Hospital
2019	**Rilapladib** (SB-659032)	**Inflammation**	lipoprotein associated phospholipase A2 selective inhibitor, acting via anti-inflammation actions	NCT01428453	II	discontinued [71]	GSK
2018	**Saracatinib** (AZD0530)	**Neuroprotectant / Antioxidant**	inhibits Fyn and Src family kinases with resultant impacts on synaptotoxicity; may impact Aβ and tau	NCT02167256	II	discontinued [72]	Yale Univ.
2018	**LY3202626**	**Aβ production**	BACE Inhibitor	NCT02791191	II	trial terminated based on futility analysis, discontinued [73]	Eli Lilly
2018	**BI 409306** (SUB 166499)	**Symptomatic**	PDE 9A inhibitor which increases cGMP levels to modulate glutamate, and impact synaptic transmission and plasticity	NCT02240693 NCT02337907	II	no significant efficacy, discontinued [74, 75]	Boehringer Ingelheim
2018	**ORM-12741** (DB 105)	**Symptomatic**	α 2c adrenergic receptor antagonist	NCT01324518	II	discontinued [76]	Orion
2017	**S47445** (CX1632)	**Symptomatic**	AMPA glutamate receptor agonist	NCT02626572	II	no significant efficacy, discontinued [77, 78]	Institut de Recherches Internationales Servier
2016	**Exenatide**	**Energy utilization**	glucagon-like peptide-1 receptor agonist approved for diabetes	NCT01255163	II	no efficacy, trial terminated; AstraZeneca withdrew support [79]	NIA
2016	**Ladostigil** (TV3326)	**Symptomatic**	rivastigmine and rasagiline combination; inhibitor of AChE, butyrylcholinesterase and MAOs; potential neuroprotective activity	NCT01429623 NCT01354691	II	no significant efficacy, discontinued [80, 81]	Avraham
2016	**MK-7622**	**Symptomatic**	muscarinic ACh positive allosteric modulator	NCT01852110	II	trial terminated based on futility analysis, discontinued [82]	Merck Sharp & Dohme
2016	**Bexarotene**	**Aβ plaque formation**	retinoid x receptor agonist, removes soluble Aβ	NCT01782742	II	primary outcome was negative [83]	Cleveland Clinic
2016	**PF-05212377** (SAM-760)	**Symptomatic**	5-HT 6 receptor antagonist	NCT01712074	II	trial terminated due to futility analysis, no significant efficacy, discontinued [84, 85]	Pfizer

Failure Year	Compound	MOA Class	MOA Description	Clinical Trial #	Ph	Results and Notes	Main Sponsor
2015	**VI-1121**	**Tau**	no additional information is available	NCT01428362	II	discontinued [86]	VIVUS
2015	**CERE-110**	**Neural growth / Regeneration**	nerve growth factor gene therapy	NCT00876863	II	discontinued [87]	Sangamo
2015	**Sembragiline** (RO4602522, RG1577)	**Symptomatic**	MAO-B inhibitor	NCT01677754	II	discontinued [88, 89]	Roche
2015	**ST101** (ZSET1446)	**Symptomatic**	ACh stimulant, may Aβ generation by modulating APP cleavage	NCT00842816 NCT00842673	II	discontinued [90]	Sonexa
2015	**GSK239512**	**Symptomatic**	histamine H3 receptor antagonist	NCT01009255	II	no significant efficacy, discontinued [91, 92]	GSK
2014	**Affitope AD02**	**Aβ vaccine**	active immunotherapy, peptide mimics N-terminus of Aβ	NCT01117818 NCT02008513	II	no significant efficacy, discontinued [93, 94]	Affiris
2014	**AZD3480** (Ispronicline, TC-1734)	**Symptomatic**	nicotinic ACh receptor selective agonist	NCT00501111 NCT01466088 NCT00109564	II	did not meet POC, discontinued [95, 96]	AstraZeneca, Targacept
2014	**NIC5-15** (Pinitol)	**Energy utilization**	cyclic sugar alcohol, insulin sensitizer, may modulate γ-secretase	NCT00470418 NCT01928420	II	no longer in company pipeline [97]	Humanetics
2014	**ABT-126** (Nelonicline)	**Symptomatic**	nicotinic ACh receptor allosteric modulator	NCT01527916 NCT01549834 NCT00948909	II	no significant efficacy, discontinued [98-100]	AbbVie
2014	**ABT-288**	**Symptomatic**	histamine H3 receptor antagonist	NCT01018875	II	terminated based on futility analysis, discontinued [101, 102]	AbbVie
2014	**ABT-384**	**Inflammation**	HSD type 1 selective inhibitor	NCT01137526	II	terminated based on futility analysis, discontinued [103, 104]	AbbVie
2014	**PF-04447943**	**Symptomatic**	PDE 9A inhibitor which increases cGMP levels to modulate glutamate, and impact synaptic transmission and plasticity	NCT00930059	II	no significant efficacy, discontinued [105, 106]	Pfizer
2013	**Vanutide cridificar** (ACC-001, PF-05236806)	**Aβ vaccine**	active immunotherapy, conjugate of multiple short Aβ fragments	NCT00959192 NCT00752232 NCT01227564 NCT01284387 NCT00479557 NCT00498602	II	no significant efficacy, discontinued [107, 108]	Pfizer, Janssen
2013	**LY2886721**	**Aβ production**	BACE inhibitor	NCT01561430	I/II	trial terminated based on adverse events, discontinued [109]	Eli Lilly
2013	**SAR 110894**	**Symptomatic**	histamine H3 receptor antagonist	NCT01266525	II	discontinued [110]	Sanofi
2012	**Avagacestat** (BMS-708163)	**Aβ production**	γ-secretase inhibitor	NCT00810147 NCT00890890	II	no significant efficacy, discontinued [111-113]	BMS
2012	**Tideglusib** (NP031112, NP12)	**Tau**	inhibitor of tau hyperphosphorylation via glycogen synthase kinase 3	NCT01350362 NCT00948259	I/II or II	no significant efficacy, discontinued [114, 115]	Noscira

Failure Year	Compound	MOA Class	MOA Description	Clinical Trial #	Ph	Results and Notes	Main Sponsor
2012	**MK 0249**	**Symptomatic**	histamine H3 receptor inverse agonist	NCT00420420	II	no significant efficacy, discontinued [116, 117]	Merck Sharp & Dohme
2012	**Lornoxicam**	**Inflammation**	NSAID	NCT01117948	II	trial terminated due to lack of efficacy, discontinued [118]	JSW
2012	**Ponezumab** (PF-04360365)	**Aβ plaque formation**	elevates plasma $A\beta_{40}$ levels	NCT00945672 NCT00722046	II	discontinued [119]	Pfizer
2011	**AZD1446** (TC-6683)	**Symptomatic**	nicotinic ACh receptor agonist	NCT01039701	II	discontinued [120]	AstraZeneca
2011	**Cerlapirdine** (SAM-531)	**Symptomatic**	5-HT 6 receptor antagonist	NCT00895895	II	trial terminated, discontinued [121]	Pfizer
2011	**Varenicline** (CP-526,555)	**Symptomatic**	nicotinic ACh receptor partial agonist	NCT00744978	II	no significant efficacy, discontinued [122, 123]	Pfizer
2011	**ELND005** (AZD-103)	**Aβ plaque formation**	neutralize low-N Aβ oligomers and prevent their aggregation	NCT00568776	II	no sign of efficacy [124]	OPKO
2010	**RG3487** (RO5313534, MEM 3454)	**Symptomatic**	nicotinic ACh receptor partial agonist	NCT00884507 NCT00454870	II	discontinued [125]	Roche, Memory
2009	**Pozanicline** (ABT-089)	**Symptomatic**	nicotinic ACh receptor partial agonist	NCT00555204 NCT00069849	II	trials terminated based on futility analysis, discontinued [126, 127]	Abbott
2009	**Etazolate** (EHT0202)	**Aβ production**	APP secretase inhibitor, also GABA-A receptor modulator and PDE-4 inhibitor	NCT00880412	II	discontinued [128]	Exonhit
2009	**Radequinil** (AC-3933)	**Symptomatic**	GABA-A receptor partial inverse agonist	NCT00359944	II	discontinued [129]	Sunovion
2009	**MK-677**	**Hormone treatment**	growth hormone secretagogue, potent inducer of IGF-1 secretion	NCT00074529	II	no significant efficacy [130]	Merck Sharp & Dohme
2008	**HF0220**	**Inflammation**	steroid, potential neuroprotective agent	NCT00357357	II	discontinued [131]	Hunter-Fleming
2008	**SSR180711C**	**Symptomatic**	nicotinic ACh receptor agonist	NCT00602680	II	trial terminated due to insufficient expected benefit risk, no longer in company pipeline [132]	Sanofi
2008	**MK0952**	**Symptomatic**	PDE 4 inhibitor which impacts cAMP levels	NCT00362024	II	trial terminated, discontinued [133]	Merck Sharp & Dohme
2008	**AVE1625** (Drinabant)	**Other**	cannabinoid receptor 1 antagonist, may impact tau phosphorylation	NCT00380302	I/II	discontinued [134]	Sanofi
2008	**GTS-21** (DMXB-A)	**Symptomatic**	nicotinic ACh receptor agonist	NCT00414622	II	discontinued [135]	CoMentis
2008	**MEM 1003** (BAY Z 4406)	**Vascular burden**	L-type Ca2+ channel antagonist	NCT00257673	II	discontinued [136]	Memory
2008	**SGS 742** (CGP-36742, DVD-742)	**Symptomatic**	GABA-B receptor antagonist	NCT00093951	II	discontinued [137]	Saegis

Failure Year	Compound	MOA Class	MOA Description	Clinical Trial #	Ph	Results and Notes	Main Sponsor
2008	**TRx 0014** (Rember TM)	**Tau**	prevents tau aggregation or dissolve existing aggregates	NCT00515333	II	discontinued [138]	TauRx
2008	**ONO-2506PO** (Arundic acid)	**Neuroprotectant / Antioxidant**	astrocyte modulators, cyclo-oxygenase 2 inhibitors, free radical scavenger	NCT00083421	II	discontinued [139]	Ono
2007	**SR57667B** (Paliroden)	**Neural growth / Regeneration**	neurotrophic, activates synthesis of endogenous neurotrophins	NCT00285025	II	discontinued [140]	Sanofi
2006	**FK962**	**Hormone treatment**	enhancer of somatostatin release	NCT00087724	II	trial terminated, discontinued [141]	Astellas
2006	**CX516** (Ampalex)	**Symptomatic**	AMPA glutamate receptor mediator	NCT00040443 NCT00001662	II	discontinued [142]	RespireRx, NINDS
2006	**NS 2330** (Tesofensine)	**Symptomatic**	MAO inhibitor which inhibits dopamine, serotonin and noradrenaline reuptake	NCT00153010	II	discontinued [143]	Boehringer Ingelheim
2005	**Mifepristone**	**Inflammation**	glucocorticoid antagonist	NCT00105105	II	trial terminated, discontinued [144, 145]	Corcept

Reported year of compound failure is a “best estimate” based on the publicly available information, as at times sponsors delay reporting the trial failure or do not report it at all; the most recent failure year is reported. Compound name includes alternate names, if any, in brackets. MOA (mechanism of action) class and description are based on weight of the evidence, as in some cases the MOA is not well understood or multiple potential mechanisms were listed.

5-HT, Serotonin; Aβ, amyloid-β, ACh, acetylcholine; AChE, acetylcholinesterase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; APP, amyloid precursor protein; BACE, β-secretase; cAMP, cyclic adenosine monophosphate; HSD, 11-β-hydroxysteroid dehydrogenase; IGF, insulin-like growth factor; MAO, monoamine oxidase; NSAID, non-steroidal anti-inflammatory drug; NINDS, National Institute of Neurological Disorders and Stroke; PDE, phosphodiesterase.

REFERENCES

[1] Eli Lilly (2020) *Lilly Announces Topline Results for Solanezumab from the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) Study*. https://investor.lilly.com/news-releases/news-release-details/lilly-announces-topline-results-solanezumab-dominantly-inherited, Accessed December, 2021.

[2] Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E, Liu-Seifert H, Mohs R, Alzheimer's Disease Cooperative Study Steering Committee; Solanezumab Study Group (2014) Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med* **370**, 311–321.

[3] Siemers ER, Sundell KL, Carlson C, Case M, Sethuraman G, Liu-Seifert H, Dowsett SA, Pontecorvo MJ, Dean RA, Demattos R (2016) Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients. *Alzheimers Dement* **12**, 110–120.

[4] Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, Hager K, Andreasen N, Scarpini E, Liu-Seifert H, Case M, Dean RA, Hake A, Sundell K, Poole Hoffmann V, Carlson C, Khanna R, Mintun M, DeMattos R, Selzler KJ, Siemers E (2018) Trial of solanezumab for mild dementia due to Alzheimer's disease. *N Engl J Med* **378**, 321–330.

[5] Roche (2020) *Roche provides topline results from investigator-led Phase II/III trial with gantenerumab in rare inherited form of Alzheimer's disease*. https://www.roche.com/de/media/releases/med-cor-2020-02-10, Accessed December, 2021.

[6] Ostrowitzki S, Lasser RA, Dorflinger E, Scheltens P, Barkhof F, Nikolcheva T, Ashford E, Retout S, Hofmann C, Delmar P, Klein G, Andjelkovic M, Dubois B, Boada M, Blennow K, Santarelli L, Fontoura P, SCarlet RoAD Investigators (2017) A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. *Alzheimers Res Ther* **9**, 95.

[7] Biogen (2019) *Eisai and Biogen to Discontinue Phase III Clinical Studies of BACE Inhibitor Elenbecestat in Early Alzheimer's Disease*. https://investors.biogen.com/news-releases/news-release-details/eisai-and-biogen-discontinue-phase-iii-clinical-studies-bace, Accessed December, 2021.

[8] Alzheimer Research Forum, Elenbecestat, https://www.alzforum.org/therapeutics/elenbecestat, Accessed December, 2021.

[9] Roche (2019) *Roche to discontinue Phase III CREAD 1 and 2 clinical studies of crenezumab in early Alzheimer's disease (AD) - other company programmes in AD continue*. https://www.roche.com/media/releases/med-cor-2019-01-30, Accessed December, 2021.

[10] Novartis (2019) *Novartis Q3 and 9M 2019 Condensed Condensed Interim Financial Report – Supplementary Data*. https://www.novartis.com/sites/novartis_com/files/2019-10-interim-financial-report-en.pdf, Accessed December, 2021.

[11] Novartis (2019) *Novartis, Amgen and Banner Alzheimer's Institute discontinue clinical program with BACE inhibitor CNP520 for Alzheimer's prevention*. https://www.novartis.com/news/media-releases/novartis-amgen-and-banner-alzheimers-institute-discontinue-clinical-program-bace-inhibitor-cnp520-alzheimers-prevention, Accessed December, 2021.

[12] VTv Therapeutics (2018) *vTv Therapeutics Announces Topline Results from the First STEADFAST Phase 3 Study Evaluating Azeliragon in People with Mild Alzheimer's Disease*. https://ir.vtvtherapeutics.com/news-releases/news-release-details/vtv-therapeutics-announces-topline-results-first-steadfast-phase, Accessed December, 2021.

[13] Janssen (2018) *Update on Janssen's BACE Inhibitor Program*. https://www.janssen.com/neuroscience/update-janssens-bace-inhibitor-program, Accessed December, 2021.

[14] Wessels AM, Tariot PN, Zimmer JA, Selzler KJ, Bragg SM, Andersen SW, Landry J, Krull JH, Downing AM, Willis BA, Shcherbinin S, Mullen J, Barker P, Schumi J, Shering C, Matthews BR, Stern RA, Vellas B, Cohen S, MacSweeney E, Boada M, Sims JR (2019) Efficacy and safety of lanabecestat for treatment of early and mild Alzheimer disease: The AMARANTH and DAYBREAK-ALZ randomized clinical trials. *JAMA Neurol* **77**, 199–209.

[15] Alzheimer Research Forum, Lanabecestat, https://www.alzforum.org/therapeutics/azd3293, Accessed December, 2021.

[16] Egan MF, Kost J, Tariot PN, Aisen PS, Cummings JL, Vellas B, Sur C, Mukai Y, Voss T, Furtek C, Mahoney E, Harper Mozley L, Vandenberghe R, Mo Y, Michelson D (2018) Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. *N Engl J Med* **378**, 1691–1703.

[17] Egan MF, Mukai Y, Voss T, Kost J, Stone J, Furtek C, Mahoney E, Cummings JL, Tariot PN, Aisen PS, Vellas B, Lines C, Michelson D (2019) Further analyses of the safety of verubecestat in the phase 3 EPOCH trial of mild-to-moderate Alzheimer's disease. *Alzheimers Res Ther* **11**, 68.

[18] Alzheimer Research Forum, Verubecestat, https://www.alzforum.org/therapeutics/verubecestat, Accessed December, 2021..

[19] Egan MF, Kost J, Voss T, Mukai Y, Aisen PS, Cummings JL, Tariot PN, Vellas B, van Dyck CH, Boada M, Zhang Y, Li W, Furtek C, Mahoney E, Harper Mozley L, Mo Y, Sur C, Michelson D (2019) Randomized trial of verubecestat for prodromal Alzheimer's disease. *N Engl J Med* **380**, 1408–1420.

[20] Takeda (2018) *Takeda and Zinfandel Pharmaceuticals Discontinue TOMMORROW Trial Following Planned Futility Analysis*. https://www.takeda.com/newsroom/newsreleases/2018/takeda-tommorrow-trial/, Accessed December, 2021.

[21] Lawlor B, Segurado R, Kennelly S, Olde Rikkert MGM, Howard R, Pasquier F, Börjesson-Hanson A, Tsolaki M, Lucca U, Molloy DW, Coen R, Riepe MW, Kálmán J, Kenny RA, Cregg F, O'Dwyer S, Walsh C, Adams J, Banzi R, Breuilh L, Daly L, Hendrix S, Aisen P, Gaynor S, Sheikhi A, Taekema DG, Verhey FR, Nemni R, Nobili F, Franceschi M, Frisoni G, Zanetti O, Konsta A, Anastasios O, Nenopoulou S, Tsolaki-Tagaraki F, Pakaski M, Dereeper O, de la Sayette V, Sénéchal O, Lavenu I, Devendeville A, Calais G, Crawford F, Mullan M, NILVAD Study Group (2018) Nilvadipine in mild to moderate Alzheimer disease: A randomised controlled trial. *PLoS Med* **15**, e1002660.

[22] Cerecin (2017) *Accera Announces Results of its First Phase 3 Study in Mild-to-Moderate Alzheimer's Disease*. https://www.cerecin.com/newsroom/accera-announces-results-of-its-first-phase-3-study.html, Accessed December, 2021.

[23] Atri A, Frölich L, Ballard C, Tariot PN, Molinuevo JL, Boneva N, Windfeld K, Raket LL, Cummings JL (2018) Effect of idalopirdine as adjunct to cholinesterase inhibitors on change in cognition in patients with Alzheimer disease: three randomized clinical trials. *JAMA* **319**, 130–142.

[24] Alzheimer Research Forum, Idalopirdine, https://www.alzforum.org/therapeutics/idalopirdine, Accessed December, 2021.

[25] Axovant (2017) *Axovant Announces Negative Topline Results of Intepirdine Phase 3 Mindset Trial in Alzhheimer's Disease*. http://investors.axovant.com/news-releases/news-release-details/axovant-announces-negative-topline-results-intepirdine-phase-3, Accessed December, 2021.

[26] Alzheimer Research Forum, Intepirdine, https://www.alzforum.org/therapeutics/intepirdine, Accessed December, 2021.

[27] AdisInsight, SK-PC-B70M, https://adisinsight.springer.com/drugs/800029407, Accessed December, 2021.

[28] Gauthier S, Feldman HH, Schneider LS, Wilcock GK, Frisoni GB, Hardlund JH, Moebius HJ, Bentham P, Kook KA, Wischik DJ, Schelter BO, Davis CS, Staff RT, Bracoud L, Shamsi K, Storey JMD, Harrington CR, Wischik CM (2016) Efficacy and safety of tau-aggregation inhibitor therapy in patients with mild or moderate Alzheimer's disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial. *Lancet* **388**, 2873–2884.

[29] Alzheimer Research Forum, LMTM, https://www.alzforum.org/therapeutics/lmtm, Accessed December, 2021.

[30] Alzheimer Research Forum, Encenicline, https://www.alzforum.org/therapeutics/encenicline, Accessed December, 2021.

[31] Relkin NR, Thomas RG, Rissman RA, Brewer JB, Rafii MS, van Dyck CH, Jack CR, Sano M, Knopman DS, Raman R, Szabo P, Gelmont DM, Fritsch S, Aisen PS, Study ADC (2017) A phase 3 trial of IV immunoglobulin for Alzheimer disease. *Neurology* **88**, 1768–1775.

[32] Alzheimer Research Forum, Gammagard®, https://www.alzforum.org/therapeutics/gammagardr, Accessed December, 2021.

[33] Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, He F, Sun X, Thomas RG, Aisen PS, Committee ADCSS, Siemers E, Sethuraman G, Mohs R, Semagacestat Study Group (2013) A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med* **369**, 341–350.

[34] Alzheimer Research Forum, Semagacestat, https://www.alzforum.org/therapeutics/semagacestat, Accessed December, 2021.

[35] Decourt B, Drumm-Gurnee D, Wilson J, Jacobson S, Belden C, Sirrel S, Ahmadi M, Shill H, Powell J, Walker A, Gonzales A, Macias M, Sabbagh MN (2017) Poor safety and

tolerability hamper reaching a potentially therapeutic dose in the use of thalidomide for Alzheimer's disease: results from a double-blind, placebo-controlled trial. *Curr Alzheimer Res* **14**, 403–411.

[36] Molloy DW, Standish TI, Zhou Q, Guyatt G, Group DS (2013) A multicenter, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: the DARAD trial. *Int J Geriatr Psychiatry* **28**, 463–470.

[37] Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Ferris S, Reichert M, Ketter N, Nejadnik B, Guenzler V, Miloslavsky M, Wang D, Lu Y, Lull J, Tudor IC, Liu E, Grundman M, Yuen E, Black R, Brashear HR, Bapineuzumab 301 and 302 Clinical Trial Investigators (2014) Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med* **370**, 322–333.

[38] Liu E, Schmidt ME, Margolin R, Sperling R, Koeppe R, Mason NS, Klunk WE, Mathis CA, Salloway S, Fox NC, Hill DL, Les AS, Collins P, Gregg KM, Di J, Lu Y, Tudor IC, Wyman BT, Booth K, Broome S, Yuen E, Grundman M, Brashear HR, Bapineuzumab 301 and 302 Clinical Trial Investigators (2015) Amyloid-β 11C-PiB-PET imaging results from 2 randomized bapineuzumab phase 3 AD trials. *Neurology* **85**, 692–700.

[39] Alzheimer Research Forum, Bapineuzumab, https://www.alzforum.org/therapeutics/bapineuzumab, Accessed December, 2021.

[40] Vandenberghe R, Rinne JO, Boada M, Katayama S, Scheltens P, Vellas B, Tuchman M, Gass A, Fiebach JB, Hill D, Lobello K, Li D, McRae T, Lucas P, Evans I, Booth K, Luscan G, Wyman BT, Hua L, Yang L, Brashear HR, Black RS, Bapineuzumab 3000 and 3001 Clinical Study Investigators (2016) Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. *Alzheimers Res Ther* **8**, 18.

[41] DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, Lopez OL, Burke G, Carlson MC, Fried LP, Kuller LH, Robbins JA, Tracy RP, Woolard NF, Dunn L, Snitz BE, Nahin RL, Furberg CD, Ginkgo Evaluation of Memory (GEM) Study Investigators (2008) Ginkgo biloba for prevention of dementia: a randomized controlled trial. *JAMA* **300**, 2253–2262.

[42] Vellas B, Coley N, Ousset P-J, Berrut G, Dartigues J-F, Dubois B, Grandjean H, Pasquier F, Piette F, Robert P, Touchon J, Garnier P, Mathiex-Fortunet H, Andrieu S, GuidAge

Study Group (2012) Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. *Lancet Neurol* **11**, 851–859.

[43] Gold M, Alderton C, Zvartau-Hind M, Egginton S, Saunders AM, Irizarry M, Craft S, Landreth G, Linnamägi U, Sawchak S (2010) Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. *Dement Geriatr Cogn Disord* **30**, 131–146.

[44] Harrington C, Sawchak S, Chiang C, Davies J, Donovan C, Saunders AM, Irizarry M, Jeter B, Zvartau-Hind M, van Dyck CH, Gold M (2011) Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-moderate Alzheimer's disease: two phase 3 studies. *Curr Alzheimer Res* **8**, 592–606.

[45] Sano M, Bell KL, Galasko D, Galvin JE, Thomas RG, van Dyck CH, Aisen PS (2011) A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. *Neurology* **77**, 556–563.

[46] Wharton W, Baker LD, Gleason CE, Dowling M, Barnet JH, Johnson S, Carlsson C, Craft S, Asthana S (2011) Short-term hormone therapy with transdermal estradiol improves cognition for postmenopausal women with Alzheimer's disease: results of a randomized controlled trial. *J Alzheimers Dis* **26**, 495–505.

[47] Alzheimer Research Forum, Estrogen, https://www.alzforum.org/therapeutics/estrogen, Accessed December, 2021.

[48] Pfizer (2010) *Pfizer and Medivation Announce Results From Two Phase 3 Studies in Dimebon (Latrepirdine) Alzheimer's Disease Clinical Development Program*. https://www.pfizer.com/news/press-release/press-release-detail/pfizer_and_medivation_announce_results_from_two_phase_3_studies_in_dimebon_latrepirdine_alzheimer_s_disease_clinical_development_program, Accessed December, 2021.

[49] Alzheimer Research Forum, Dimebon, https://www.alzforum.org/therapeutics/dimebon, Accessed December, 2021.

[50] Sanofi (2016) *A randomized, multicenter, double-blind, placebo-controlled, 18-month study of the efficacy of xaliproden in patients with mild-to-moderate dementia of the Alzheimer's type (NCT00104013)*. https://www.sanofi.com/-/media/Project/One-Sanofi-

Web/Websites/Global/Sanofi-COM/Home/common/docs/clinical-study-results/efc2724-summary.pdf, Accessed December, 2021.

[51] Porzner M, Müller T, Seufferlein T (2009) SR 57746A/xaliproden, a non-peptide neurotrophic compound: prospects and constraints for the treatment of nervous system diseases. *Expert Opin Investig Drugs* **18**, 1765–1772.

[52] Sanofi (2016) *A randomized, multicenter, double-blind, placebo-controlled, 18-month study of the efficacy of xaliproden in patients with mild-to-moderate dementia of the Alzheimer's type (NCT00103649)*. https://www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/common/docs/clinical-study-results/efc2946-summary.pdf, Accessed December, 2021.

[53] AdisInsight, Lecozotan, https://adisinsight.springer.com/drugs/800019708, Accessed December, 2021.

[54] Mohs RC, Shiovitz TM, Tariot PN, Porsteinsson AP, Baker KD, Feldman PD (2009) Atomoxetine augmentation of cholinesterase inhibitor therapy in patients with Alzheimer disease: 6-month, randomized, double-blind, placebo-controlled, parallel-trial study. *Am J Geriatr Psychiatry* **17**, 752–759.

[55] Alzheimer Research Forum, Atomoxetine, https://www.alzforum.org/therapeutics/atomoxetine, Accessed December, 2021.

[56] Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, Zavitz KH, Tarenflurbil Phase 3 Study Group (2009) Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. *JAMA* **302**, 2557–2564.

[57] Alzheimer Research Forum, Tarenflurbil, https://www.alzforum.org/therapeutics/flurizan, Accessed December, 2021.

[58] Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, Schwam E, Schindler R, Hey-Hadavi J, DeMicco DA, Breazna A, LEADe Investigators (2010) Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology* **74**, 956–964.

[59] de Jong D, Jansen R, Hoefnagels W, Jellesma-Eggenkamp M, Verbeek M, Borm G, Kremer B (2008) No effect of one-year treatment with indomethacin on Alzheimer's disease progression: a randomized controlled trial. *PLoS One* **3**, e1475–e1475.

[60] Lyketsos CG, Breitner JCS, Green RC, Martin BK, Meinert C, Piantadosi S, Sabbagh M (2007) Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. *Neurology* **68**, 1800–1808.

[61] Group AR, Martin BK, Szekely C, Brandt J, Piantadosi S, Breitner JCS, Craft S, Evans D, Green R, Mullan M (2008) Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. *Arch Neurol* **65**, 896–905.

[62] Group A-FR (2015) Follow-up evaluation of cognitive function in the randomized Alzheimer's Disease Anti-inflammatory Prevention Trial and its follow-up study. *Alzheimers Dement* **11**, 216–25.e1.

[63] Aisen PS, Gauthier S, Ferris SH, Saumier D, Haine D, Garceau D, Duong A, Suhy J, Oh J, Lau WC, Sampalis J (2011) Tramiprosate in mild-to-moderate Alzheimer's disease - a randomized, double-blind, placebo-controlled, multi-centre study (the Alphase Study). *Arch Med Sci* **7**, 102–111.

[64] Alzheimer Research Forum, Alzhemed™, https://www.alzforum.org/therapeutics/alzhemedtm, Accessed December, 2021.

[65] Henderson VW, Ala T, Sainani KL, Bernstein AL, Stephenson BS, Rosen AC, Farlow MR (2015) Raloxifene for women with Alzheimer disease: A randomized controlled pilot trial. *Neurology* **85**, 1937–1944.

[66] Steyer R (2004) Forest Labs Off on Alzheimer's Bust. *TheStreet*. https://www.thestreet.com/investing/stocks/forest-labs-off-on-alzheimers-bust-10180912, Accessed December, 2021.

[67] Biogen (2021) *Biogen Announces Topline Results From Phase 2 Study of Gosuranemab, an Anti-Tau Antibody, for Alzheimer's Disease*. http://media.biogen.com/news-releases/news-release-details/biogen-announces-topline-results-phase-2-study-gosuranemab-anti, Accessed December, 2021.

[68] Alzheimer Research Forum, Tilavonemab, https://www.alzforum.org/therapeutics/tilavonemab, Accessed December, 2021.

[69] Alzheimer Research Forum, Zagotenemab, https://www.alzforum.org/therapeutics/zagotenemab, Accessed December, 2021.

[70] AdisInsight, DCB-AD1, https://adisinsight.springer.com/drugs/800044401, Accessed

December, 2021.

[71] AdisInsight, Rilapladib - GlaxoSmithKline, https://adisinsight.springer.com/drugs/800018454, Accessed December, 2021.

[72] Alzheimer Research Forum, Saracatinib, https://www.alzforum.org/therapeutics/saracatinib, Accessed December, 2021.

[73] Alzheimer Research Forum, LY3202626, https://www.alzforum.org/therapeutics/ly3202626, Accessed December, 2021.

[74] Frölich L, Wunderlich G, Thamer C, Roehrle M, Garcia MJ, Dubois B (2019) Evaluation of the efficacy, safety and tolerability of orally administered BI 409306, a novel phosphodiesterase type 9 inhibitor, in two randomised controlled phase II studies in patients with prodromal and mild Alzheimer's disease. *Alzheimers Res Ther* **11**, 18.

[75] Alzheimer Research Forum, BI 409306, https://www.alzforum.org/therapeutics/bi-409306#:~:text=BI%20409306%20is%20an%20inhibitor,neurotransmitters%20nitric%20oxide%20and%20glutamate., Accessed December, 2021.

[76] AdisInsight, DB 105, https://adisinsight.springer.com/drugs/800029247, Accessed December, 2021.

[77] Bernard K, Gouttefangeas S, Bretin S, Galtier S, Robert P, Holthoff-Detto V, Cummings J, Pueyo M (2019) A 24-week double-blind placebo-controlled study of the efficacy and safety of the AMPA modulator S47445 in patients with mild to moderate Alzheimer's disease and depressive symptoms. *Alzheimers Dement (N Y)* **5**, 231–240.

[78] Alzheimer Research Forum, S47445, https://www.alzforum.org/therapeutics/s47445#:~:text=S47445%20is%20being%20developed%20for,previously%20generated%20CX516%2C%20now%20discontinued., Accessed December, 2021.

[79] Alzheimer Research Forum, Exenatide, https://www.alzforum.org/therapeutics/exenatide, Accessed December, 2021.

[80] Schneider LS, Geffen Y, Rabinowitz J, Thomas RG, Schmidt R, Ropele S, Weinstock M (2019) Low-dose ladostigil for mild cognitive impairment: A phase 2 placebo-controlled clinical trial. *Neurology* **93**, e1474–e1484.

[81] Alzheimer Research Forum, Ladostigil, https://www.alzforum.org/therapeutics/ladostigil, Accessed December, 2021.

[82] Alzheimer Research Forum, MK-7622, https://www.alzforum.org/therapeutics/mk-7622, Accessed December, 2021.

[83] Cummings JL, Zhong K, Kinney JW, Heaney C, Moll-Tudla J, Joshi A, Pontecorvo M, Devous M, Tang A, Bena J (2016) Double-blind, placebo-controlled, proof-of-concept trial of bexarotene Xin moderate Alzheimer's disease. *Alzheimers Res Ther* **8**, 1–9.

[84] Fullerton T, Binneman B, David W, Delnomdedieu M, Kupiec J, Lockwood P, Mancuso J, Miceli J, Bell J (2018) A Phase 2 clinical trial of PF-05212377 (SAM-760) in subjects with mild to moderate Alzheimer's disease with existing neuropsychiatric symptoms on a stable daily dose of donepezil. *Alzheimers Res Ther* **10**, 38.

[85] Alzheimer Research Forum, PF-05212377, https://www.alzforum.org/therapeutics/pf-05212377, Accessed December, 2021.

[86] AdisInsight, VI-1121, https://adisinsight.springer.com/drugs/800034968, Accessed December, 2021.

[87] Alzheimer Research Forum, CERE-110, https://www.alzforum.org/therapeutics/cere-110, Accessed December, 2021.

[88] Nave S, Doody RS, Boada M, Grimmer T, Savola J-M, Delmar P, Pauly-Evers M, Nikolcheva T, Czech C, Borroni E, Ricci B, Dukart J, Mannino M, Carey T, Moran E, Gilaberte I, Muelhardt NM, Gerlach I, Santarelli L, Ostrowitzki S, Fontoura P (2017) Sembragiline in moderate Alzheimer's disease: results of a randomized, double-blind, placebo-controlled phase II trial (MAyflOwer RoAD). *J Alzheimers Dis* **58**, 1217–1228.

[89] Alzheimer Research Forum, Sembragiline, https://www.alzforum.org/therapeutics/sembragiline, Accessed December, 2021.

[90] AdisInsight, ST101, https://adisinsight.springer.com/drugs/800019838, Accessed December, 2021.

[91] Grove RA, Harrington CM, Mahler A, Beresford I, Maruff P, Lowy MT, Nicholls AP, Boardley RL, Berges AC, Nathan PJ, Horrigan JP (2014) A randomized, double-blind, placebo-controlled, 16-week study of the H3 receptor antagonist, GSK239512 as a monotherapy in subjects with mild-to-moderate Alzheimer's disease. *Curr Alzheimer Res* **11**, 47–58.

[92] Alzheimer Research Forum, GSK239512, https://www.alzforum.org/therapeutics/gsk239512, Accessed December, 2021.

[93] Schneeberger A, Hendrix S, Mandler M, Ellison N, Bürger V, Brunner M, Frölich L, Mimica N, Hort J, Rainer M, Imarhiagbe D, Kurz A, Peters O, Gertz H-J, Tierney L, Mattner F, Schmidt W, Dubois B (2015) Results from a phase II study to assess the clinical and immunological activity of AFFITOPE® AD02 in patients with early Alzheimer's disease. *J Prev Alzheimers Dis* **2**, 103–114.

[94] Alzheimer Research Forum, Affitope AD02, https://www.alzforum.org/therapeutics/affitope-ad02, Accessed December, 2021.

[95] AdisInsight, Ispronicline, https://adisinsight.springer.com/drugs/800011083, Accessed December, 2021.

[96] Frölich L, Ashwood T, Nilsson J, Eckerwall G (2011) Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: a phase IIb dose-finding study. *J Alzheimers Dis* **24**, 363–374.

[97] Humanetics Corporation, NIC5-15, https://www.humaneticscorp.com/pipeline, Accessed December, 2021.

[98] Gault LM, Lenz RA, Ritchie CW, Meier A, Othman AA, Tang Q, Berry S, Pritchett Y, Robieson WZ (2016) ABT-126 monotherapy in mild-to-moderate Alzheimer's dementia: randomized double-blind, placebo and active controlled adaptive trial and open-label extension. *Alzheimers Res Ther* **8**, 44.

[99] Florian H, Meier A, Gauthier S, Lipschitz S, Lin Y, Tang Q, Othman AA, Robieson WZ, Gault LM (2016) Efficacy and safety of ABT-126 in subjects with mild-to-moderate Alzheimer's disease on stable doses of acetylcholinesterase inhibitors: a randomized, double-blind, placebo-controlled study. *J Alzheimers Dis* **51**, 1237–1247.

[100] Alzheimer Research Forum, Nelonicline, https://www.alzforum.org/therapeutics/nelonicline, Accessed December, 2021.

[101] Haig GM, Pritchett Y, Meier A, Othman AA, Hall C, Gault LM, Lenz RA (2014) A randomized study of H3 antagonist ABT-288 in mild-to-moderate Alzheimer's dementia. *J Alzheimers Dis* **42**, 959–971.

[102] Alzheimer Research Forum, ABT-288, https://www.alzforum.org/therapeutics/abt-288, Accessed December, 2021.

[103] Marek GJ, Katz DA, Meier A, Greco N 4th, Zhang W, Liu W, Lenz RA (2014) Efficacy and safety evaluation of HSD-1 inhibitor ABT-384 in Alzheimer's disease. *Alzheimers*

Dement **10**, S364-73.

[104] Alzheimer Research Forum, ABT-384, https://www.alzforum.org/therapeutics/abt-384, Accessed December, 2021.

[105] Schwam EM, Nicholas T, Chew R, Billing CB, Davidson W, Ambrose D, Altstiel LD (2014) A multicenter, double-blind, placebo-controlled trial of the PDE9A inhibitor, PF-04447943, in Alzheimer's disease. *Curr Alzheimer Res* **11**, 413–421.

[106] AdisInsight, PF-04447943, https://adisinsight.springer.com/drugs/800028797, Accessed December, 2021.

[107] Pasquier F, Sadowsky C, Holstein A, Leterme GLP, Peng Y, Jackson N, Fox NC, Ketter N, Liu E, Ryan JM (2016) Two phase 2 multiple ascending-dose studies of vanutide cridificar (ACC-001) and QS-21 adjuvant in mild-to-moderate Alzheimer's disease. *J Alzheimers Dis* **51**, 1131–1143.

[108] Alzheimer Research Forum, Vanutide cridificar, https://www.alzforum.org/therapeutics/vanutide-cridificar, Accessed December, 2021.

[109] Eli Lilly (2013) *Lilly Voluntarily Terminates Phase II Study for LY2886721, a Beta Secretase Inhibitor, Being Investigated as a Treatment for Alzheimer's Disease*. https://investor.lilly.com/news-releases/news-release-details/lilly-voluntarily-terminates-phase-ii-study-ly2886721-beta, Accessed December, 2021.

[110] AdisInsight, SAR 110894, https://adisinsight.springer.com/drugs/800025936, Accessed December, 2021.

[111] Coric V, van Dyck CH, Salloway S, Andreasen N, Brody M, Richter RW, Soininen H, Thein S, Shiovitz T, Pilcher G, Colby S, Rollin L, Dockens R, Pachai C, Portelius E, Andreasson U, Blennow K, Soares H, Albright C, Feldman HH, Berman RM (2012) Safety and tolerability of the γ-secretase inhibitor avagacestat in a phase 2 study of mild to moderate Alzheimer disease. *Arch Neurol* **69**, 1430–1440.

[112] Coric V, Salloway S, van Dyck CH, Dubois B, Andreasen N, Brody M, Curtis C, Soininen H, Thein S, Shiovitz T, Pilcher G, Ferris S, Colby S, Kerselaers W, Dockens R, Soares H, Kaplita S, Luo F, Pachai C, Bracoud L, Mintun M, Grill JD, Marek K, Seibyl J, Cedarbaum JM, Albright C, Feldman HH, Berman RM (2015) Targeting prodromal Alzheimer disease with avagacestat: a randomized clinical trial. *JAMA Neurol* **72**, 1324–1333.

[113] Alzheimer Research Forum, Avagacestat, https://www.alzforum.org/therapeutics/avagacestat, Accessed December, 2021.

[114] Lovestone S, Boada M, Dubois B, Hüll M, Rinne JO, Huppertz H-J, Calero M, Andrés M V, Gómez-Carrillo B, León T, del Ser T (2015) A phase II trial of tideglusib in Alzheimer's disease. *J Alzheimers Dis* **45**, 75–88.

[115] Alzheimer Research Forum, Tideglusib, https://www.alzforum.org/therapeutics/tideglusib, Accessed December, 2021.

[116] Egan M, Yaari R, Liu L, Ryan M, Peng Y, Lines C, Michelson D (2012) Pilot randomized controlled study of a histamine receptor inverse agonist in the symptomatic treatment of AD. *Curr Alzheimer Res* **9**, 481–490.

[117] AdisInsight, MK 0249, https://adisinsight.springer.com/drugs/800024706, Accessed December, 2021.

[118] Alzheimer Research Forum, Lornoxicam, https://www.alzforum.org/therapeutics/lornoxicam, Accessed December, 2021.

[119] Alzheimer Research Forum, Ponezumab, https://www.alzforum.org/therapeutics/ponezumab, Accessed December, 2021.

[120] Alzheimer Research Forum, AZD1446, https://www.alzforum.org/therapeutics/azd1446, Accessed December, 2021.

[121] AdisInsight, Cerlapirdine, https://adisinsight.springer.com/drugs/800025908, Accessed December, 2021.

[122] Kim SY, Choi SH, Rollema H, Schwam EM, McRae T, Dubrava S, Jacobsen J (2014) Phase II crossover trial of varenicline in mild-to-moderate Alzheimer's disease. *Dement Geriatr Cogn Disord* **37**, 232–245.

[123] Alzheimer Research Forum, Varenicline, https://www.alzforum.org/therapeutics/varenicline, Accessed December, 2021.

[124] Salloway S, Sperling R, Keren R, Porsteinsson AP, van Dyck CH, Tariot PN, Gilman S, Arnold D, Abushakra S, Hernandez C, Crans G, Liang E, Quinn G, Bairu M, Pastrak A, Cedarbaum JM (2011) A phase 2 randomized trial of ELND005, scyllo-inositol, in mild to moderate Alzheimer disease. *Neurology* **77**, 1253–1262.

[125] AdisInsight, RG3487, https://adisinsight.springer.com/drugs/800022293, Accessed December, 2021.

[126] Lenz RA, Pritchett YL, Berry SM, Llano DA, Han S, Berry DA, Sadowsky CH, Abi-Saab WM, Saltarelli MD (2015) Adaptive, dose-finding phase 2 trial evaluating the safety and efficacy of ABT-089 in mild to moderate Alzheimer disease. *Alzheimer Dis Assoc Disord* **29**, 192–199.

[127] AdisInsight, Pozanicline, https://adisinsight.springer.com/drugs/800006779, Accessed December, 2021.

[128] AdisInsight, Etazolate, https://adisinsight.springer.com/drugs/800016925, Accessed December, 2021.

[129] AdisInsight, Radequinil, https://adisinsight.springer.com/drugs/800010724, Accessed December, 2021.

[130] Sevigny JJ, Ryan JM, van Dyck CH, Peng Y, Lines CR, Nessly ML (2008) Growth hormone secretagogue MK-677: no clinical effect on AD progression in a randomized trial. *Neurology* **71**, 1702–1708.

[131] AdisInsight, HF0220, https://adisinsight.springer.com/drugs/800016847, Accessed December, 2021.

[132] ClinicalTrials.gov, Clinical pharmacology and therapeutics, Effect on Cognitive Performance and Safety/Tolerability of SSR180711C in Mild Alzheimer's Disease, https://clinicaltrials.gov/ct2/show/NCT00602680?term=NCT00602680&draw=2&rank=1, Accessed December, 2021.

[133] AdisInsight, MK 0952, https://adisinsight.springer.com/drugs/800024701, Accessed December, 2021.

[134] AdisInsight, Drinabant - Opiant Pharmaceuticals, https://adisinsight.springer.com/drugs/800020616, Accessed December, 2021.

[135] AdisInsight, GTS 21, https://adisinsight.springer.com/drugs/800005633, Accessed December, 2021.

[136] Alzheimer Research Forum, MEM 1003, https://www.alzforum.org/therapeutics/mem-1003, Accessed December, 2021.

[137] Alzheimer Research Forum, SGS 742, https://www.alzforum.org/therapeutics/sgs-742, Accessed December, 2021.

[138] Alzheimer Research Forum, Rember TM, https://www.alzforum.org/therapeutics/rember-tm, Accessed December, 2021.

[139] AdisInsight, Arundic acid, https://adisinsight.springer.com/drugs/800011094, Accessed December, 2021.

[140] AdisInsight, Paliroden, https://adisinsight.springer.com/drugs/800013042, Accessed December, 2021.

[141] Astellas (2006) *Astellas Discontinues Development of Alzheimer's Disease Compound FK962*. https://www.astellas.com/system/files/news/2018-06/060718-1_eg_0.pdf, Accessed December, 2021.

[142] Alzheimer Research Forum, CX516, https://www.alzforum.org/therapeutics/cx516, Accessed December, 2021.

[143] Alzheimer Research Forum, NS2330, https://www.alzforum.org/therapeutics/ns2330, Accessed December, 2021.

[144] ClinicalTrials.gov, Mifepristone as Adjunctive Therapy in Alzheimer's Disease, https://clinicaltrials.gov/ct2/results?cond=&term=NCT00105105&cntry=&state=&city=&dist=, Accessed December, 2021.

[145] AdisInsight, Mifepristone - Corcept Therapeutics, https://adisinsight.springer.com/drugs/800001657, Accessed December, 2021.